WO 2002/094317

05/18/01 PRO
05/17/02 PCT/GIP

THAT WHICH IS CLAIMED: 1-22

4/5/5

1. A method for treating an immune system disorder in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

A-RECEPTOR ANTAGO

$192740
$208240 *
1031109
2002137887

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to treat the immune system disorder.

2. The method of Claim 1 wherein the disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

NOT AN I.S. DISORDER

3. A method according to Claim 1, wherein the A_1 adenosine receptor antagonist is an antibody that binds the A_1 adenosine receptor.

4. A method according to Claim 1, wherein the P_{2X} purinoceptor antagonist is an antibody that binds the P_{2X} purinoceptor.

5. A method for preventing or delaying the onset of an immune system disorder in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to prevent or delay the onset of the immune system disorder that would occur in the absence of the administration.

P_2 - PURINOCEPTORS
P2X RECEPTORS
P2X-SELECTIVE LIGANDS
HIV
ADA

ADENOSINE-1
A1 ADENOSINE RECEPTORS
A1 RECEPTOR
A1-SELECTIVE LIGANDS

NOT AN I.S. DISORDER

6. The method of Claim 5 wherein the disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

7. The method according to Claim 5, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

8. A method according to Claim 5, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

9. A method for treating HIV infection or AIDS in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to treat the HIV infection or AIDS.

10. The method of Claim 9, wherein the treatment is carried out in conjunction with another treatment for HIV infection or AIDS.

11. A method according to Claim 9, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

12. A method according to Claim 9, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

13. A method for preventing or delaying the onset of HIV infection or AIDS in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to prevent or delay the onset of the HIV infection or AIDS that would occur in the absence of the administration.

14. A method according to Claim 13, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

15. A method according to Claim 13, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

16. A method for treating adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to treat adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

17. The method of Claim 16, wherein the treatment is carried out in conjunction with another treatment for adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

18. A method according to Claim 16, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

19. A method according to Claim 16, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

20. A method for preventing or delaying the onset of adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to prevent or delay the onset of the adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) that would occur in the absence of the administration.

21. A method according to Claim 20, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

22. A method according to Claim 20, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 November 2002 (28.11.2002)

PCT

(10) International Publication Number
WO 02/094317 A1

(51) International Patent Classification[7]: A61K 39/395

(21) International Application Number: PCT/US02/15854

(22) International Filing Date: 17 May 2002 (17.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/292,072 18 May 2001 (18.05.2001) US

(71) Applicant *(for all designated States except US)*: ENDACEA INC. [US/US]; PO Box 12076, Research Triangle Park, NC 27709 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: WILSON, Constance, Neely [US/US]; PO Box 12076, Research Triangle Park, NC 27709 (US).

(74) Agent: MYERS BIGEL SIBLEY & SAJOVEC; PO Box 37428, Raleigh, NC 27627 (US).

(81) Designated States *(national)*: AU, CA, JP, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/094317 A1

(54) Title: METHODS AND FORMULATIONS OF USING A1 ADENOSINE AND P2X PURINORECEPTOR ANTAGONISTS

(57) Abstract: A_1 adenosine receptor antagonists and P_2X receptor antagonists are useful in the treatments of disorders of the immune system, which include HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

METHODS AND FORMULATIONS OF USING A1 ADENOSINE AND P2X PURINORECEPTOR ANTAGONISTS

Field of the Invention

The present invention relates to methods for the treatment and prevention of disorders of the immune system, and in particular for the treatment and prevention of HIV infection and AIDS.

Background of the Invention

Purinergic receptors can be classified into the P_1 (adenosine) receptors and the P_2 (adenosine 5' triphosphate) receptors. Adenosine receptors can further be delineated into major subclasses, the A_1, A_2 (A_{2a} and A_{2b}) and A_3 adenosine receptors. These subtypes are differentiated by molecular structure, radioligand binding profiles, and by pharmacological activity and signal transduction mechanisms. Binding of adenosine, a naturally occurring nucleoside, to specific adenosine receptors leads to either stimulation (A_2-receptor activation) or inhibition (A_1-receptor activation) of adenylate cyclase activity, resulting in an increase or decrease of intracellular cAMP, respectively. Most tissues and cell types possess either the A_1 or A_2 receptor, or both. Specific A_1, A_2, and A_3 adenosine receptor antagonists and agonists are known. *See, e.g.,* Trivedi et al., *Structure-Activity Relationships of Adenosine A_1 and A_2 Receptors, In*: Adenosine and Adenosine Receptors, M. Williams, Ed., Humana Press, Clifton, New Jersey, USA (1990); Jacobson et al., *J. Medicinal Chem.* 35, 407 (1992); Fredholm et al., *Pharm. Rev.* 46, 143 (1994); Jacobson, Abstracts from Purines '96, *Drug Dev. Res.*, March 1996, page 112.

Based on potency profiles of structural analogues for ATP, ATP-sensitive (P_2) purinoreceptors have been subclassified into P_{2X} and P_{2Y} purinoceptors. With few exceptions, P_{2X} receptors are located on vascular smooth muscle cells and mediate

vasoconstriction, while P_{2Y} receptors are generally located on endothelial cells and mediate vasodilation. Burnstock and Kennedy, *Gen. Pharmacol.* 16:433 (1985; Ralevic et al., *Br. J. Pharmacol.* 103:1108 (1991).

Inflammatory cells, including monocytes and alveolar macrophages express the A_1, A_2 and A_3 adenosine receptor subtypes. Eppell et al., *J. Immunology* 143:4141 (1989); Lapin and Whaley, *Clin. Exp. Immunol.* 57:454 (1984); Saijadi, et al., *J. Immunol.* 156:3435 (1996). The presence of A_1 adenosine receptors on human monocytes/macrophages is known. *See* J. E. Salmon, *J. Immunology* **151**,2775-2785, 1993. Mature monocytes enter the circulatory system from the bone marrow; some monocytes enter tissues and develop into macrophages in the spleen, lymph nodes, liver, lung, thymus, peritoneum, nervous system, skin and other tissues. Both monocytes and macrophages play a role in inflammatory responses and secrete various proteins active in immune and inflammatory responses, including tumor necrosis factor (TNF) and interleukin-1 (IL-1)). Upon stimulation, monocytes and macrophages can generate various oxygen metabolites, including superoxide anion and H_2O_2, which are toxic to both pathogens and normal cells. A_1 adenosine receptors are also present on human lymphocytes and PMNs.

A_2 adenosine receptors are present on human B and T (OKT4+ and OKT8+) lymphocytes, PMNs, monocytes, basophils, and platelets, where they inhibit superoxide anion generation by PMNs, histamine release from human basophils, and platelet aggregation. A_{2a} receptors have been identified as the predominantly expressed subtype of adenosine receptors in T cells. It has been suggested that A_{2a} receptors are involved in adenosine-mediated immunosuppression under adenosine deaminase (ADA) deficiency conditions *in vivo*. M. Koshiba *et al.*, *J. Biol. Chem.* **272**, 25881-25889 (1997).

Accumulation of adenosine and of deoxyadenosine in the absence of adenosine deaminase activity (ADA) activity results in lymphocyte depletion and in severe combined immunodeficiency (ADA SCID). Patients with adenosine deaminase deficiency and severe combined immunodeficiency have markedly impaired lymphocyte proliferation and antibody synthesis. These patients have also been find to have an increased intracellular concentration of ATP and elevated levels of plasma adenosine. Schwartz et al., earlier found that immunological defects in severe combined immunodeficiency and adenosine deaminase deficiency may result in part from excessive cyclic AMP synthesis associated with overstimulation of the

adenosine receptor-adenylcyclase pathway. A. L. Schwartz et al., *Clin. Immunol. Immunopathol.* **9**, 499-505 (1978). Other groups have determined that adenosine deaminase can prevent the accumulation of adenosine in thymocytes. Thymic adenosine concentrations of mice treated with an ADA inhibitor were elevated over 30-fold, and adenosine concentrations in mice treated with an ADA inhibitor are sufficient to cause adenosine receptor-mediated thymocyte apoptosis *in vitro*, suggesting that adenosine accumulation could play a role in ADA-deficient severe combined immunodeficiency R. Resta et al. *J. Clin. Invest.* **99**, 676-683 (1997). In ADA SCID and severe immunodeficiency disease (SCID), however, there is a lack of correlation between ADA replacement treatment and clinical effects.

Based on numerous findings, these observed effects of extracellular adenosine are likely to be mediated by A_{2a} receptor-mediated signaling . *See* S. Huang et al., *Blood* **90**, 1600-1610 (1997). It has also been suggested that abnormal signaling through purinergic receptors by extracellular adenosine (accumulated because of cell surface-associated ADA deficiency) could cause the apoptosis of T cells and to eliminate those subpopulations of cells that express apoptotic signal-transducing P_1 receptors. Moreover, apoptosis of thymocytes by ATP is Ca^{2+} independent, suggesting involvement of P_{2X} receptors. S. Apasov et. al., *Immunol. Rev.* **146**, 5 (1995).

Human Immunodeficiency Virus (HIV, formerly and occasionally referred to, as lymphadenopathy-associated virus, LAV, and human-T-lymphotropic virus, HTLV, and acquired immune deficiency syndrome (AIDS) related virus, ARV), is generally recognized as causing acquired immunodeficiency syndrome, or AIDS. At least two HIV viruses, HIV-1 and HIV-2, have been identified as AIDS infective agents. Levels of ADA isoenzyme levels in sera of patients with AIDS are higher than those in healthy controls, while ADA activity in infected cells is promoted by HIV-1 infection. I. Tsuboi, *Clin. Diag. Lab. Immunol.* **2**, 626, 1995.

HIV is cytopathic for T lymphocytes expressing CD4 (OKT 4) antigen, but not OKT 8. Both adenosine and HIV decrease the expression of CD4 antigen on cell surface of human T cells. The HIV genome contains a polyadenylated 3' end that can contact adenosine receptors on human leukocytes. HIV virions may contact the adenosine receptors of cells surface in certain steps of the infection. The adsorption of virus to its cellular receptor (CD4 antigen) can activate indirectly adenosine receptors resulting in a decrease of CD4 expression, which is regarded as an

adenosine receptor related phenomenon. Therefore, pretreatment of cells with adenosine, and the activation of A_2 receptors, reduces the expression of CD4 antigens available for the viruses in their binding to the cells. See S. Sipka *et al.*, *Acta Biochim. Biophys., Hung.* **23**, 75, 1988

Several chemokine receptors have been shown to act as coreceptors for HIV-1 entry into cells of different lineages. CCR5 is expressed in primary monocytes, macrophages, primary T cells, and granulocyte precursors. Individuals with mutations of CCR5 expression show resistance to HIV-1 infection. Agents which increase cAMP down-regulate CCR5 expression in monocyte-derived macrophages and impair the capacity of M-tropic HIV-1 isolates to infect treated cells. M. Thivierge et al., *Blood* **92,** 40 (1998).

During all stages of HIV infection, tissue macrophages provide a unique viral reservoir. In these cells, HIV persistently replicates in the absence of cytopathicity, escapes immune surveillance, and spreads via cell-to-cell contact. It has been suggested that the persistence of HIV in macrophages may be NF-κB dependent. NF-κB is a heterodimeric protein and transcription factor, anchored in the cytosol by an inhibitory protein, IκB. Following cell activation by a number of extracellular stimuli, IκBα undergoes hyperphosphorylation event that renders the molecule susceptible to degradation. This process results in the release of NF-κB, which undergoes nuclear translocation and drives gene transcription. Human macrophages express constitutive level of NF-κB in nuclei in the absence of exogenous cellular activation. Persistent HIV replication in human macrophages or monocytes upregulates NF-κB activity. The half-life of IκBα in HIV-infected cells is reduced by at least 50% compared to that in uninfected cells, and this fact directly correlates with increased levels of the nuclear pool of NF-κB in HIV-infected cells. The Iκκ complex kinase activity is selectively activated in is shown to mediate increased NF-κB activation in HIV-infected cells. *See* S. Asin , et al., *J. Virology* **73,** 3893 (1999).

The mechanism whereby HIV infection induces activation of NF-κB in cells of monocyte lineage remains unknown. Understanding the mechanism to inhibit HIV virus-induced activation of NF-κB may decrease viral persistence in these cells and eliminate them as a potential reservoir of HIV replication in infected patients.

Summary of the Invention

It has now been found that administration of compositions containing A_1 adenosine receptor antagonists and/or P_{2X} purinoceptor antagonists, or a combination thereof, can prevent or inhibit of immune system disorders. Although the Applicant does not wish to be bound to any particularly theory of the invention, it is believed that A_1 adenosine receptor antagonists prevent or delay the entry of HIV virus into cells. A_1 adenosine receptor antagonists also appear to prevent HIV-induced upregulation of chemokine receptors in monocytes, macrophages and T cells, activation of NF-κB in monocytes and macrophages, activation of nuclear A1 adenosine receptors and nuclear PKC in the spleen, and HIV-1 gene expression in the spleen.

Moreover, ATP may serve as a contact-to-contact mediator for monocytes/macrophages and aid in the infection of these cells with HIV by serving as a phosphate donor, and may upregulate chemokine coreceptors for HIV on these cells via P_{2X} purinoceptor activation.

In view of the foregoing, certain embodiments of the present invention relate to methods for treating an immune system disorder in a subject in need of such treatment. As a second aspect, the present invention relates to methods for preventing an immune system disorder in a subject in need of such treatment. In one embodiment, the method comprises administering to the subject an A_1 adenosine receptor antagonist in amount effective to treat the disorder of immune deficiency. In another embodiment, the method comprises administering to the subject an A_1 adenosine receptor antagonist in amount effective to prevent the immune system disorder. In preferred embodiments, the immune system disorder is HIV infection or AIDS. In other preferred embodiments, the immune system disorder is adenosine deaminase deficiency-dependent severe combined immunodeficiency (ADA SCID).

The present inventor has also discovered that administration of a P_{2X} purinoceptor antagonist is useful as a treatment for immune system disorders. Thus, certain embodiments of the invention relate to methods of treating an immune system disorder in a subject in need to such treatment, the method comprising administering to a subject a P_{2X} purinoceptor antagonist in amount effective to treat the immune system disorder. In preferred embodiments, the immune system

disorder is HIV infection or AIDS. In other preferred embodiments, the immune system disorder is adenosine deaminase deficiency-dependent severe combined immunodeficiency (ADA SCID).

The present invention further provides a method of treating certain disorders of the immune system by administering an effective amount of a composition or compound comprising at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist. In certain embodiments of the invention, the compound administered is both an A_1 adenosine receptor antagonist and a P_{2X} purinoceptor antagonist.

As an additional aspect, the present invention provides pharmaceutical formulations comprising for the treatment of immune disorders comprising an A_1 adenosine receptor antagonist, and/or a P_{2X} purinoceptor antagonist; or a combination thereof, together with a pharmaceutically acceptable carrier.

The foregoing and other aspects of the present invention are explained in detail in the specification set forth below.

Brief Description of the Drawings

Detailed Description of the Invention

The present invention will now be described with reference to the accompanying figures, in which preferred embodiments of the invention are illustrated. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The methods and formulations of the present invention are useful in treating disorders of the immune system (*i.e.*, immunodeficiencies). Immunodeficiencies are generally categorized as either acquired immunodeficiencies or inherited immunodeficiencies. Acquired immunodeficiencies include human immunodeficiency virus-1 (HIV-1) infection, herpes virus infections, Epstein-Barr virus infections, lepromatous leprosy and diminished immune capacity resulting from skin burns in burn patients, *i.e.* burn-related immunodeficiency. Inherited immunodeficiencies include several genetically different forms of SCID, including adenosine deaminase deficiency dependent SCID (ADA SCID), SCID autosomal recessive with and without B cells (no ADA deficiency), SCID X-linked recessive without B cells, SCID autosomal recessive (with ADA deficiency), purine nucleotide phosphorylase deficiency (PNP SCID), severe combined immune deficiency (IL-2 receptor deficiency (*i.e.* X-LINKED SCID), and bare lymphocyte syndrome. Other immunodeficiencies include various forms of congenital or genetically determined hematopoietic abnormalities, several high risk leukemias and several forms of severe life-threatening aplastic anemia. Still other immunodeficiencies that may be treated by methods and formulations of the present invention include Wiskott-Aldrich syndrome; Blackfan-Diamond syndrome; Fanconi anemia; severe neutrophil dysfunction; chronic granulomatous disease of childhood; severe (Kostman-type) agranulocytosis; immunodeficiency and neutropenia of cartilage-hair hypoplasia; infantile and late onset osteopetrosis; aplastic anemia-toxic chemical, idiopathic, immunological, and genetic (non-Fanconi); acute myeloid leukemia; chronic myeloid leukemia; Burkitt lymphoma, and recurrent acute lymphatic leukemia.

In preferred embodiments of the invention, the immune system disorder that is treated is HIV infection or AIDS. In other preferred embodiments, the immune system disorder that is treated is adenosine deaminase deficiency-dependent severe combined immunodeficiency (ADA SCID).

Agents that bind to A_1 adenosine receptors are well known to those of skill in the art. One of the best known classes of adenosine receptor antagonists are the xanthines, which include caffeine and theophylline. *See e.g.*, Müller et al., *J. Med. Chem.* **33**, 2822 (1990). Numerous A_1 adenosine receptors antagonists have been synthesized. For example, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) is a highly selective A_1 adenosine receptor antagonist with negligible nonspecific binding (less than 1%) in tissues (Jacobson et al., *J. Med. Chem.* 35:407 (1992); Bruns, RF

"Adenosine Receptor Binding Assays", Receptor Biochemistry and Methodology, Volume II: Adenosine Receptors, DMF Cooper and C. Londos (Eds.), Alan Liss, Inc., New York, NY 1988, pp. 43-62). Other examples of A_1 adenosine receptor antagonists include, but are not limited to, xanthine amine congener (XAC); xanthine carboxylic congener (XCC); 1,3-dipropyl-xanthines such as 1,3-dipropyl-8-(-3-noradamantyl) xanthine (KW 3902), 1,3-dipropyl-8-(dicyclopropylmethyl) xanthine (KF 15372), 1,3-dipropyl-8-[2-(5,6-epoxy)norbonyl]xanthine (ENX), 8-(1-aminocyclopentyl)-1,3-dipropylxanthine (IRFI 117), 1,3-dipropyl-8-(3-noradamantyl) xanthine (NAX) and 1,3-dipropyl-8-(3-oxocyclopentyl) xanthine (KFM 19); 1-propyl-3-(4-amino)-3-phenethyl)-8-cyclopentylxanthine (BW-A844U); 1,3-dipropyl-8-sulfophenylxanthine (DPSPX); cyclopentyl theophylline (CPT) and 7-[2-ethyl (2-hydroxyethyl)amino]-ethyl]-3,7-dihydro-1,3-dimethyl-8-(phenylmethyl)-1H-purine-2, 6-dione (Bamifylline); N^6, 9-methyl adenines such as (±)-N^6-endonorboman-2-yl-9-methyladenine (N-0861) and 8-(N-methylisopropyl) amino- N^6- (5'-endohydroxy-endonorbornyl)-9-methyladenine (WRC-0571); N^6, 9-disubstituted adenines; 2-phenyl-7-deazaadenines such as (R)-7,8-dimethyl-2-phenyl-9-(1-phenylethyl)-7-deazaadenine; 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-*i*]purin-5(4*H*)-one; (±)R-1-[(,)-3[2-[phenylpyrazolo (1,5-a) pyridin-3-yl]acryloyl]-2-piperidine ethanol; 8-azaxanthines such as 7-cyclopentyl-1,3-dipropyl-8-azaxanthine; tetrahydrobenzothiophenones such as ethyl-3-(benzylthio)-4-oxo-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate; N-6-cyclopentyl-3'-substituted xylo-furanosyl adenosines (Van Calinbergh, *J. Med. Chem.* 40:3765, November 1997).

Additionally, selective analogues of adenosine receptor antagonists have been developed through the "functionalized congener" approach. Analogues of adenosine receptor ligands bearing functionalized chains have been synthesized and attached covalently to various organic moieties such as amines and peptides. Jacobson et al. *J. Med. Chem.* 35:408 (1992) has proposed various derivatives of adenosine and theophylline for use as receptor antagonists.

Antibodies raised against the A_1 adenosine receptor that selectively target and bind to this receptor can also be used as A_1 adenosine receptor antagonists. Such antibodies targeted to the A_1 adenosine receptor can be produced routinely in accordance with well known methods of antibody production. As used herein, the term "A_1 adenosine receptor antagonist" encompasses antibodies that selectively or

specifically bind to the receptor, when such antibodies are used for their antagonist effects.

P_{2X} purinoceptor antagonists are known in the art; an example of a selective P_{2X} purinoceptor antagonist is pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS). Additional specific pharmacological antagonists of purinoceptors have been described by Humphrey et al., *Naunyn-Schmied. Arch. Pharmacol.* 352:585 (1995); Abracchio and Burnstock, *Pharmac. Ther.* 64:445 (1994); Bultmann et al., *Naunyn-Schmied. Arch. Pharmacol.* 354:481 (1996); and Bultmann et al., *Naunyn-Schmied. Arch. Pharmacol.* 354:498 (1996). Antibodies raised against the P_{2X} purinoceptor that selectively target and bind to this receptor can also be used as P_{2X} purinoceptor antagonists. Such antibodies targeted to the P_{2X} purinoceptor can be produced routinely in accordance with well known methods of antibody production. As used herein, the term " P_{2X} purinoceptor antagonist" encompasses antibodies that selectively or specifically bind to the receptor, when such antibodies are used for their antagonist effects.

The compounds of the present invention may optionally be provided and administered in the form of a free base, or may be in the form of a pharmaceutically acceptable salt thereof. Suitable pharmacuetically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methansulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt and N,N´-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt.

The present invention provides methods of preventing and treating disorders of the immune system, wherein an effective amount of an A_1 adenosine receptor antagonist, a P_{2X} purinoceptor antagonist, or a combination thereof, is administered to a subject in need of such treatment. A single compound that antagonizes both the A_1 receptor and the P_{2X} purinoceptor may also be used in the methods of the present invention.

By the terms "treating " or "treatment" of the immune system disorder, it is intended that the severity of the disorder or the symptoms of the disorder are reduced, or the disorder is partially or entirely eliminated, as compared to that which would occur in the absence of treatment. Treatment does not require the achievement of a complete cure of the disorder.

By the terms "preventing" or "prevention" the immune system disorder, it is intended that the inventive methods eliminate or reduce the incidence or onset of the disorder, as compared to that which would occur in the absence of treatment. Alternatively stated, the present methods slow, delay, control, or decrease the likelihood or probability of the disorder in the subject, as compared to that which would occur in the absence of treatment.

An "effective amount" is that amount able to reduce the severity, development, or onset of the disorder that would occur in the absence of the antagonists, or slow the progress (over time) of the disorder, compared to that which would occur in the absence of said antagonists. The term "effective amount" also refers to a concentration of an A_1 adenosine receptor antagonist, P_{2X} purinoceptor antagonist, or combination thereof, which is sufficient to interfere with pathological changes caused by the disorder. Preferably, the A_1 adenosine receptor antagonist is a selective A_1 adenosine receptor antagonist. Also preferably, the P_{2X} purinoceptor antagonist is a selective P_{2X} purinoceptor antagonist.

The therapeutically effective dosage of any specific compound, the use of which is in the scope of the present invention, will vary somewhat from compound to compound, patient to patient, and will depend upon the condition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 20 mg/kg body weight will have therapeutic efficacy, with still higher dosages potentially being employed for oral and/or aerosol administration. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, all weights being calculated based upon the weight of the active base, including the cases where salt is employed. Typically a dosage from about 0.56 mg/kg to about 5 mg/kg will be employed. In certain circumstances, higher or lower doses may be also appropriate. The daily dose can be administered either by a single dose in the form of an individual dosage unit or several smaller dosage units or by multiple administration of subdivided dosages at certain intervals.

The methods of the present invention may be carried out in conjunction with other treatments for the immune system disorder. For example, pharmaceutical compositions known to be useful in the treatment of HIV infection and AIDS may be administered concurrently with the A_1 antagonists or P_{2X} purinoreceptor antagonists of the present invention. Alternatively, a course of treatment known to be useful in the treatment of HIV infection and AIDS may be carried out while a course of treatment utilizing the present invention is also carried out.

The present invention also provides pharmaceutical formulations, both for veterinary and for human medical use, which comprise the active compounds of the invention, together with one or more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof. Pharmaceutically acceptable carriers, include but are not limited to, saline, water, dextrose and water, cyclodextrins or similar sugar solutions, low dose sodium hydroxide solutions, propylene glycol, and polyethylene glycol.

The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic or parenteral (including subcutaneous, intramuscular and intravenous) administration. Formulations suitable for aerosol, oral and parenteral administration are preferred.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the integrase inhibiting agent as a powder or granules; or a suspension in an aqueous liquor or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a

suitable machine, with the active compound being in a free-flowing form such as a powder or granules which is optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tables comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound, which is preferably isotonic with the blood of the recipient and pyrogen-free.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

In yet another aspect of the present invention, there is provided an injectable, stable, sterile composition comprising an active compound or compounds of the present invention, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for injection thereof into the subject. The unit dosage form typically comprises from about 10 mg to about 10 grams of the compound or salt. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent which is physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidyl choline.

Further, the present invention provides liposomal formulations of the compounds of present invention. The technology for forming liposomal suspensions is well known in the art. When the compound is an aqueous-soluble salt, using conventional liposome technology, the same may be incorporated into lipid vesicles. In such an instance, due to the water solubility of the compound or salt, the compound or salt will be substantially entrained within the hydrophilic center or core of the liposomes. The lipid layer employed may be of any conventional composition and may either contain cholesterol or may be cholesterol-free. When the compound or salt of interest is water-insoluble, again employing conventional liposome formation technology, the salt may be substantially entrained within the hydrophobic lipid bilayer which forms the structure of the liposome. In either instance, the

liposomes which are produced may be reduced in size, as through the use of standard sonication and homogenization techniques.

The following Examples are provided to illustrate the present invention, and should not be construed as limiting thereof.

[EXAMPLES]

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED:

1. A method for treating an immune system disorder in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to treat the immune system disorder.

2. The method of Claim 1 wherein the disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

3. A method according to Claim 1, wherein the A_1 adenosine receptor antagonist is an antibody that binds the A_1 adenosine receptor.

4. A method according to Claim 1, wherein the P_{2X} purinoceptor antagonist is an antibody that binds the P_{2X} purinoceptor.

5. A method for preventing or delaying the onset of an immune system disorder in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to prevent or delay the onset of the immune system disorder that would occur in the absence of the administration.

6. The method of Claim 5 wherein the disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

7. The method according to Claim 5, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

8. A method according to Claim 5, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

9. A method for treating HIV infection or AIDS in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to treat the HIV infection or AIDS.

10. The method of Claim 9, wherein the treatment is carried out in conjunction with another treatment for HIV infection or AIDS.

11. A method according to Claim 9, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

12. A method according to Claim 9, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

13. A method for preventing or delaying the onset of HIV infection or AIDS in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to prevent or delay the onset of the HIV infection or AIDS that would occur in the absence of the administration.

14. A method according to Claim 13, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

15. A method according to Claim 13, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

16. A method for treating adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to treat adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

17. The method of Claim 16, wherein the treatment is carried out in conjunction with another treatment for adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

18. A method according to Claim 16, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

19. A method according to Claim 16, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

20. A method for preventing or delaying the onset of adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of:

(a) A_1 adenosine receptor antagonists;

(b) P_{2X} purinoceptor antagonists; and

(c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist;

wherein said compound is administered in an amount effective to prevent or delay the onset of the adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) that would occur in the absence of the administration.

21. A method according to Claim 20, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

22. A method according to Claim 20, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/15854

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 39/395
US CL : 424/172.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
. U.S. : 424/172.1; 436/501, 506; 536/389.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LAMBRECHT G., Design and pharmacology of selective P2-purinoceptor antagonists..Journal of Autonomic Pharmacology 1996 Dec;16(6):341-4.	1- 22
A	LAMBRECHT G., Agonists and antagonists acting at P2X receptors: selectivity profiles and functional implications. Naunyn-Schmiedebergs Archives of Pharmacology. 2000 Nov;362(4-5):340-50.	1- 22
		1- 22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
29 July 2002 (29.07.2002)

Date of mailing of the international search report
06 SEP 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Myron G. Hill
Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US02/15854

Continuation of Item 4 of the first sheet:
Title was more than 17 words.

METHODS AND FORMULATIONS OF USING A1 ADENOSINE AND P2X PURINORECEPTOR ANTAGONISTS

Continuation of B. FIELDS SEARCHED Item 3:
WEST- US PAT, EPO, JPO, Derwent
MEDLINE
Terms- A1 adenosine receptor antagonist, P2x purinoceptor antagonist, HIV, AIDS, ADA SCID, treatment, immune disorder

METHODS AND FORMULATIONS OF USING A_1 ADENOSINE RECEPTOR ANTAGONISTS AND P_{2X} PURINOCEPTOR ANTAGONISTS FOR THE TREATMENT AND PREVENTION OF IMMUNE SYSTEM DISORDERS

Related Applications

This application is a continuation-in-part of PCT International Application No. PCT/US02/15854, filed May 17, 2002, entitled *Methods and Formulations of Using A_1 Adenosine and P_{2X} Purinoreceptor Antagonists*, which claims priority from United States Provisional Patent Application Serial No. 60/292,072, filed May 18, 2001, entitled *Methods and Formulations of Using A_1 Adenosine Receptor Antagonists and P_{2X} Purinoceptor Antagonists for the Treatment and Prevision of Immune System Disorders*, the contents of which are hereby incorporated herein by reference.

Field of the Invention

The present invention relates to methods for the treatment and prevention of disorders of the immune system, and in particular for the treatment and prevention of HIV infection and AIDS.

Background of the Invention

Purinergic receptors can be classified into the P_1 (adenosine) receptors and the P_2 (adenosine 5' triphosphate) receptors. Adenosine receptors can further be delineated into major subclasses, the A_1, A_2 (A_{2a} and A_{2b}) and A_3 adenosine receptors. These subtypes are differentiated by molecular structure, radioligand binding profiles, pharmacological activity and signal transduction mechanisms. Binding of adenosine (a naturally occurring nucleoside) to specific adenosine receptors leads to either stimulation (A_2-receptor activation) or inhibition (A_1-receptor activation) of adenylate cyclase activity, resulting in an increase or decrease of

intracellular cAMP, respectively. Most tissues and cell types possess either the A_1 or A_2 receptor, or both. Specific A_1, A_2, and A_3 adenosine receptor antagonists and agonists are known. *See, e.g.*, Trivedi et al., *Structure-Activity Relationships of Adenosine A_1 and A_2 Receptors*, in: Adenosine and Adenosine Receptors, M. Williams, Ed., Humana Press, Clifton, New Jersey, USA (1990); Jacobson et al., *J. Medicinal Chem.* **35**, 407 (1992); Fredholm et al., *Pharm. Rev.* **46**, 143 (1994); Jacobson, Abstracts from Purines '96, *Drug Dev. Res.*, March 1996, page 112.

Based on potency profiles of structural analogues for ATP, ATP-sensitive (P_2) purinoceptors have been subclassified into P_{2X} and P_{2Y} purinoceptors. Seven P_{2X} receptors belong to the most simple transmitter-gated ion channel family, and are found throughout the body in the nervous system (central and peripheral), heart, and on smooth muscle, platelets, lymphocytes and macrophages. Khakh et al., *Pharmacol. Rev.* **53**,107 (2001). P_{2X} receptors are located on vascular smooth muscle cells and mediate vasoconstriction, while P_{2Y} receptors are generally located on endothelial cells and mediate vasodilation. Burnstock and Kennedy, *Gen. Pharmacol.* **16**, 433 (1985); Ralevic et al., *Br. J. Pharmacol.* **103**,1108 (1991).

Inflammatory cells, including monocytes and alveolar macrophages, express the A_1, A_2 and A_3 adenosine receptor subtypes. Eppell et al., *J. Immunology* **143**, 4141 (1989); Lapin and Whaley, *Clin. Exp. Immunol.* **57**,454 (1984); Saijadi, et al., *J. Immunol.* **156**, 3435 (1996). The presence of A_1 adenosine receptors on human monocytes/macrophages is known. *See* J. E. Salmon, *J. Immunology* **151**, 2775 (1993). Mature monocytes enter the circulatory system from the bone marrow; some monocytes enter tissues and develop into macrophages in the spleen, lymph nodes, liver, lung, thymus, peritoneum, nervous system, skin and other tissues. Both monocytes and macrophages play a role in inflammatory responses, and secrete various proteins active in immune and inflammatory responses, including tumor necrosis factor (TNF) and interleukin-1 (IL-1). Upon stimulation, monocytes and macrophages can generate various oxygen metabolites that are toxic to both pathogens and normal cells, including superoxide anion and H_2O_2. A_1 adenosine receptors are also present on human lymphocytes and PMNs.

A_2 adenosine receptors are present on human B and T (OKT4+ and OKT8+) lymphocytes, PMNs, monocytes, basophils, and platelets, where they inhibit superoxide anion generation by PMNs, histamine release from human basophils, and platelet aggregation. A_{2a} receptors have been identified as the predominantly

expressed subtype of adenosine receptors in T cells. It has been suggested that A_{2a} receptors are involved in adenosine-mediated immunosuppression under adenosine deaminase (ADA) deficiency conditions *in vivo*. M. Koshiba *et al.*, *J. Biol. Chem.* **272**, 25881 (1997).

Accumulation of adenosine and of deoxyadenosine in the absence of adenosine deaminase activity (ADA) results in lymphocyte depletion and in severe combined immunodeficiency (ADA SCID). Patients with adenosine deaminase deficiency and severe combined immunodeficiency exhibit markedly impaired lymphocyte proliferation and antibody synthesis. These patients have also been found to have an increased intracellular concentration of ATP and elevated levels of plasma adenosine. It has been determined that immunological defects in severe combined immunodeficiency and adenosine deaminase deficiency may result in part from excessive cyclic AMP synthesis associated with overstimulation of the adenosine receptor-adenyl cyclase pathway. *See* A. L. Schwartz et al., *Clin. Immunol. Immunopathol.* **9**, 499-505 (1978). It has also been determined that adenosine deaminase can prevent the accumulation of adenosine in thymocytes. In certain studies, thymic adenosine concentrations of mice treated with an ADA inhibitor were elevated over 30-fold, and adenosine concentrations in mice treated with an ADA inhibitor are sufficient to cause adenosine receptor-mediated thymocyte apoptosis *in vitro*, suggesting that adenosine accumulation could play a role in ADA-deficient severe combined immunodeficiency. R. Resta et al. *J. Clin. Invest.* **99**, 676-683 (1997). In ADA SCID and severe immunodeficiency disease (SCID), however, there is a lack of correlation between ADA replacement treatment and clinical effects.

It has been suggested that both P_2 and P_1 purinoceptors, via transmembrane signaling, play an integral role in differentiation of immature CD4+CD8+ thymocytes into CD8+CD4- and CD4+CD8- cells, leading to the development of cytotoxic T lymphocytes (CTL) and T helper cells, and in the apoptotic processes in T cells. *See* S. Apasov et. al., *Immunol. Rev.* **146**, 5 (1995). ATP serves as a source of extracellular adenosine, as a phosphate donor, and as a transmembrane signaling ligand in both T-cell development and effector functions. It has also been suggested that extracellular ATP and extracellular phosphorylation are involved in cell-to-cell contact leading to lymphocyte activation. The presence of ecto-ATPase and Ag-receptor-induced accumulation of extracellular ATP has been demonstrated for both

T helper and CTL. Moreover, apoptosis of thymocytes by ATP is Ca^{2+} independent, suggesting involvement of P_{2X} receptors. S. Apasov et. al., *supra*.

A P_{2X} receptor identified in muscle and neuronal cells was found to be highly homologous to the RP-2 gene, which is expressed in apoptotic thymocytes. Furthermore, it has been suggested that abnormal signaling through purinoceptors by extracellular adenosine (which is accumulated because of cell surface-associated ADA deficiency) may cause the apoptosis of T cells in ADA SCID.

Human Immunodeficiency Virus (HIV), formerly and occasionally referred to as lymphadenopathy-associated virus (LAV), human-T-lymphotropic virus (HTLV), or acquired immune deficiency syndrome (AIDS)-related virus (ARV), is generally recognized as causing acquired immunodeficiency syndrome, or AIDS. At least two HIV viruses, HIV-1 and HIV-2, have been identified as AIDS infective agents. Levels of ADA isoenzyme levels in sera of patients with AIDS are higher than those in healthy controls, while ADA activity in infected cells is promoted by HIV-1 infection. I. Tsuboi, *Clin. Diag. Lab. Immunol.* **2**, 626, (1995).

HIV is cytopathic for T lymphocytes expressing CD4 (OKT 4) antigen, but not OKT 8. Both adenosine and HIV decrease the expression of CD4 antigen on the cell surface of human T cells. The HIV genome contains a polyadenylated 3' end that can contact adenosine receptors on human leukocytes. HIV virions may contact the adenosine receptors of cells surface in certain steps of the infection. The adsorption of virus to its cellular receptor (CD4 antigen) can indirectly activate adenosine receptors resulting in a decrease of CD4 expression, which is regarded as an adenosine receptor-related phenomenon. Therefore, pretreatment of cells with adenosine, and the activation of A_2 receptors, reduces the expression of CD4 antigens available for the viruses in their binding to the cells. *See* S. Sipka *et al.*, *Acta Biochim. Biophys., Hung.* **23**, 75 (1988).

Several chemokine receptors have been shown to act as coreceptors for HIV-1 entry into cells of different lineages. CCR5 is expressed in primary monocytes, macrophages, primary T cells, and granulocyte precursors. Individuals with mutations of CCR5 expression show resistance to HIV-1 infection. Agents that increase cAMP down-regulate CCR5 expression in monocyte-derived macrophages and impair the capacity of M-tropic HIV-1 isolates to infect treated cells. M. Thivierge et al., *Blood* **92**, 40 (1998).

During all stages of HIV infection, tissue macrophages provide a unique viral reservoir. In these cells, HIV persistently replicates in the absence of cytopathicity, escapes immune surveillance, and spreads via cell-to-cell contact. It has been suggested that the persistence of HIV in macrophages may be NF-κB dependent. NF-κB is a heterodimeric protein and transcription factor, anchored in the cytosol by an inhibitory protein, IκBα. Following cell activation by a number of extracellular stimuli, IκBα undergoes a hyperphosphorylation event that renders the molecule susceptible to degradation. This process results in the release of NF-κB, which undergoes nuclear translocation and drives gene transcription. In the absence of exogenous cellular activation, human macrophages express constitutive levels of NF-κB in nuclei. Persistent HIV replication in human macrophages or monocytes upregulates NF-κB activity. The half-life of IκBα in HIV-infected cells is reduced by at least 50% compared to that in uninfected cells, which directly correlates with increased levels of the nuclear pool of NF-κB in HIV-infected cells. The IκK complex kinase activity is selectively activated, and is shown to mediate increased NF-κB activation in HIV-infected cells. *See* S. Asin et al., *J. Virology* **73,** 3893 (1999).

The mechanism whereby HIV infection induces activation of NF-κB in cells of monocyte lineage remains unknown. It has been reported that activation of protein kinase C is an essential component of NF-κB mediated HIV infection. *See* S. Asin et al., *supra*. It has also been reported that CD4 glycoprotein, expressed in the surface of T helper cells and macrophages, is required for high affinity binding of HIV viral envelope glycoprotein to target cells and subsequent viral entry. Moreover, it has been shown that entry of primate lentiviruses into target cells is dependent upon the interaction of the viral envelope glycoprotein with CD4 and one or more members of the G protein-coupled receptor (GPCR) family of transmembrane proteins. *See* Unutmaz et al., *Immunology* **10**, 225 (1998). Understanding the mechanism to inhibit HIV virus-induced activation of NF-κB may decrease viral persistence in these cells and eliminate them as a potential reservoir of HIV replication in infected patients.

Adenosine receptors are members of the superfamily of GPCRs. Four subtypes, referred to as the A_1, A_{2a}, A_{2b}, and A_3 adenosine receptors, are currently recognized. *See* Olah and Stiles, *Pharmacol. Ther.* **85**, 55 (2000). A_1 adenosine receptors are coupled via G proteins to a number of effector systems, including

adenylate cyclase, phospholipase A_2 (PLA_2), phospholipase C (PLC), potassium channels, calcium channels, and guanylate cyclase. Olah and Stiles, *supra*; van Galen et al., *Medicinal Res. Rev.* **12**, 423 (1992); Akbar et al., *Molecular Pharmacol.* **45**, 1036 (1994). A_1 adenosine receptors inhibit adenylate cyclase and stimulate PLC and PLA_2 by coupling to a pertussis toxin-sensitive inhibitory G protein (G_i). Furthermore, activation of A_1 adenosine receptors increases protein kinase C activity in coronary arteries. *See* Marala and Mustafa, *Am. J. Physiol.* **268**, H271 (1995).

In different cell types, lipopolysaccharide (LPS) responses, such as cytokine release, are linked to a number of signal transduction pathways (e.g., PLA_2, PLC and adenylate cyclase), phosphorylation of proteins (e.g., protein kinase C and protein kinase A), and activation of transcription factors (e.g., NFκB). *See* Chen et al., *Current Topics in Microbiol. and Immunol.* **181**,169 (1992); Schletter et al., *Arch. Microbiol.* **164**, 383 (1995); Sweet and Hume, *J. Leukoc. Biol.* **60**, 8 (1996). The inhibitory effect of LPS on adenylate cyclase or activation of PLA_2 in macrophages is pertussis toxin sensitive, suggesting that the protein responsible for LPS activation of these signal transduction pathways is coupled to a G_i protein. *See* Chen et al., *supra*; Jakway and DeFranco, *Science* **234**, 743 (1986); Coffee et al., *Biochim. Biophys. Acta.* **1035**, 201 (1990). By coupling to a G_i protein, LPS inhibits adenylate cyclase and activates the production of arachidonic acid metabolites.

In normal human monocytes and cultured cells, heterotrimeric G proteins specifically regulate CD14-mediated, LPS-induced mitogen-activated protein kinase (MAPK) activation and cytokine production. Solomon, et al., *J. Clin. Invest.* **102**, 2019 (1998). Also, LPS-induced IL-1 production in the human promonocytic cell line U937, is linked to *de novo* synthesis of an inhibitory G protein. Daniel-Issakan et al., *J. Biol. Chem.* **264**, 20240 (1989). Moreover, the effect of LPS on arachidonic acid metabolism and TXA_2 release in rat peritoneal macrophages was found to be dependent on protein kinase C activation. Geisel et al., *Biochemica. et Biophysica. Acta.* **1085**, 15 (1991).

It has been reported that LPS is a potent stimulator of the expression of HIV-1 in monocytes and macrophages. *See* Pomerantz et al., *J. Exp. Med.* **172**, 253 (1990). It has also been reported that LPS-induced HIV-1 expression in transgenic mice is mediated by TNF-α and IL-1. *See* Tanaka et al., *AIDS* **14**,1299 (2000). In that particular study, HIV-1 gene expression was activated 10 – 20 fold by LPS and

serum p24 Gag protein levels reached 400 pg/ml, similar to those in the serum of AIDS patients. Moreover, in humans with endotoxemia, (myco)bacterial antigens, including LPS, cell wall components of *Mycobacterium tuberculosis* (lipoarabinnomannan) or *Staphylococcus aureus* (lipoteichoic acid), or staphylococcal enterotoxin B increased expression of HIV co-receptors CXCR4 and CCR5 on CD4+ Tcells. *See* Juffermans et al., *Blood* **96**, 2649 (2000). These effects of LPS on the expression of HIV-1 in monocytes and macrophages, and expression of chemokine HIV co-receptors on T cells may be mediated by A_1 adenosine receptors and P_{2X} purinoceptors. The present inventor has previously discovered that LPS binds to and activates A_1 adenosine receptors on human pulmonary artery endothelial cells (unpublished observations). Periodate oxidized adenosine 5'-triphosphate (o-ATP), a P_{2X} purinoceptor antagonist, was found to inhibit the effects of LPS on nitric oxide (NO) production, inhibit the expression of inducible nitric oxide synthase (iNOS), and inhibit NF-kappa-B-like binding activity in RAW 264.7 macrophages. Hu, et al., *J. Biol. Chem.* **273,** 27170 (1998). Finally, the P_{2X} purinoceptor antagonist, pyridoxal-phosphate-6-azophenyl-2',4'-disulphonic acid (PPADS) was found to prevent the effect of LPS on the expression of iNOS.

Summary of the Invention

It has now been found that administration of compositions comprising A_1 adenosine receptor antagonists and/or P_{2X} purinoceptor antagonists, or a combination thereof, can prevent or inhibit immune system disorders. Although the Applicant does not wish to be bound to any particular theory of the invention, it is believed that A_1 adenosine receptor antagonists prevent or delay the entry of HIV virus into cells. A_1 adenosine receptor antagonists also appear to prevent HIV-induced upregulation of chemokine receptors in monocytes, macrophages and T cells; prevent activation of NF-κB in monocytes and macrophages; prevent activation of nuclear A1 adenosine receptors and nuclear PKC in the spleen; and prevent HIV-1 gene expression in the spleen.

Moreover, ATP may serve as a contact-to-contact mediator for monocytes/macrophages and T cells, and aid in the infection of these cells with HIV by serving as a phosphate donor. ATP may also upregulate chemokine coreceptors for HIV on these cells via P_{2X} purinoceptor activation.

In view of the foregoing, certain aspects of the present invention relate to methods for treating an immune system disorder in a subject in need of such treatment. In other aspects, the present invention relates to methods for preventing an immune system disorder in a subject in need of such treatment. In one embodiment, the method comprises administering to the subject an A_1 adenosine receptor antagonist in an amount effective to treat a disorder of immune deficiency. In another embodiment, the method comprises administering to the subject an A_1 adenosine receptor antagonist in an amount effective to prevent an immune system disorder. In preferred embodiments, the immune system disorder is HIV infection or AIDS. In other preferred embodiments, the immune system disorder is adenosine deaminase deficiency-dependent severe combined immunodeficiency (ADA SCID).

The present inventor has further discovered that administration of a P_{2X} purinoceptor antagonist is useful as a treatment for immune system disorders. The present inventor has also discovered that administration of a P_{2X} purinoceptor antagonist is useful in methods of preventing immune system disorders. Thus, certain embodiments of the invention relate to methods of treating an immune system disorder in a subject in need of such treatment, the method comprising administering to a subject a P_{2X} purinoceptor antagonist in an amount effective to treat the immune system disorder. Other embodiments of the invention relate to methods of preventing an immune system disorder in a subject in need of such treatment, the method comprising administering to a subject a P_{2X} purinoceptor antagonist in an amount effective to prevent the immune system disorder. In preferred embodiments, the immune system disorder is HIV infection or AIDS. In other preferred embodiments, the immune system disorder is adenosine deaminase deficiency-dependent severe combined immunodeficiency (ADA SCID).

The present invention further provides a method of treating certain disorders of the immune system by administering an effective amount of a composition or compound comprising at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist. In certain embodiments of the invention, a compound administered to prevent or treat an immune disorder is both an A_1 adenosine receptor antagonist and a P_{2X} purinoceptor antagonist.

As an additional aspect, the present invention provides pharmaceutical formulations for the treatment of immune disorders comprising an A_1 adenosine

receptor antagonist, and/or a P_{2X} purinoceptor antagonist, or a combination thereof, together with a pharmaceutically acceptable carrier.

The foregoing and other aspects of the present invention are explained in detail in the description set forth below.

Detailed Description of the Invention

The present invention will now be described with reference to the accompanying figures and specification, in which preferred embodiments of the invention are illustrated. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only, and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The methods and formulations of the present invention are useful in treating disorders of the immune system (*i.e.*, immunodeficiencies). Immunodeficiencies are generally categorized as either acquired immunodeficiencies or inherited immunodeficiencies. Acquired immunodeficiencies include human immunodeficiency virus-1 (HIV-1) infection, herpes virus infections, Epstein-Barr virus infections, lepromatous leprosy and diminished immune capacity resulting from skin burns in burn patients (*i.e.* burn-related immunodeficiency). Inherited immunodeficiencies include several genetically different forms of SCID, including adenosine deaminase deficiency dependent SCID (ADA SCID), SCID autosomal recessive with and without B cells (no ADA deficiency), SCID X-linked recessive without B cells, SCID autosomal recessive (with ADA deficiency), purine nucleotide phosphorylase deficiency (PNP SCID), severe combined immune deficiency (IL-2 receptor deficiency) (*i.e.* X-linked SCID), and bare lymphocyte syndrome. Other

immunodeficiencies include various forms of congenital or genetically determined hematopoietic abnormalities, several high-risk leukemias and several forms of severe life-threatening aplastic anemia. Still other immunodeficiencies that may be treated by methods and formulations of the present invention include Wiskott-Aldrich syndrome; Blackfan-Diamond syndrome; Fanconi anemia; severe neutrophil dysfunction; chronic granulomatous disease of childhood; severe (Kostman-type) agranulocytosis; immunodeficiency and neutropenia of cartilage-hair hypoplasia; infantile and late onset osteopetrosis; aplastic anemia (toxic chemical, idiopathic, immunological, and non-Fanconi genetic); acute myeloid leukemia; chronic myeloid leukemia; Burkitt lymphoma, and recurrent acute lymphatic leukemia.

In preferred embodiments of the invention, the immune system disorder that is treated or prevented is HIV infection or AIDS. In other preferred embodiments, the immune system disorder that is treated or prevented is adenosine deaminase deficiency-dependent severe combined immunodeficiency (ADA SCID).

A_1 adenosine receptor antagonists and P_{2X} purinoceptor antagonists are referred to herein as "active compounds." As used herein, "purinoceptor," "purinergic receptor," and "purinoreceptor" are used interchangeably.

Numerous A_1 adenosine receptor antagonists are known to those of skill in the art. One known class of adenosine receptor antagonist is the xanthine family, which include caffeine and theophylline. *See e.g.*, Müller et al., *J. Med. Chem.* **33**, 2822 (1990). Numerous A_1 adenosine receptors antagonists have been synthesized. For example, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) is a highly selective A_1 adenosine receptor antagonist with negligible nonspecific binding (less than 1%) in tissues. *See* Jacobson et al., *J. Med. Chem.* **35**, 407 (1992); Bruns, RF "Adenosine Receptor Binding Assays", in Receptor Biochemistry and Methodology, Volume II: Adenosine Receptors, DMF Cooper and C. Londos (Eds.), Alan Liss, Inc., New York, NY (1988), pp. 43-62. Other examples of A_1 adenosine receptor antagonists include, but are not limited to, xanthine amine congener (XAC); xanthine carboxylic congener (XCC); 1,3-dipropyl-xanthines such as 1,3-dipropyl-8-(-3-noradamantyl) xanthine (KW 3902), 1,3-dipropyl-8-(dicyclopropylmethyl) xanthine (KF 15372), 1,3-dipropyl-8-[2-(5,6-epoxy)norbonyl]xanthine (ENX), 8-(1-aminocyclopentyl)-1,3-dipropylxanthine (IRFI 117), 1,3-dipropyl-8-(3-noradamantyl) xanthine (NAX) and 1,3-dipropyl-8-(3-oxocyclopentyl) xanthine (KFM 19); 1-propyl-3-(4-amino)-3-phenethyl)-8-cyclopentylxanthine (BW-A844U); 1,3-dipropyl-8-

sulfophenylxanthine (DPSPX); cyclopentyl theophylline (CPT) and 7-[2-ethyl (2-hydroxyethyl)amino]-ethyl]-3,7-dihydro-1,3-dimethyl-8-(phenylmethyl)-1H-purine-2, 6-dione (Bamifylline); N^6, 9-methyl adenines such as (±)-N^6-endonorbornan-2-yl-9-methyladenine (N-0861) and 8-(N-methylisopropyl) amino- N^6- (5'-endohydroxy-endonorbornyl)-9-methyladenine (WRC-0571); N^6, 9-disubstituted adenines; 2-phenyl-7-deazaadenines such as (R)-7,8-dimethyl-2-phenyl-9-(1-phenylethyl)-7-deazaadenine; 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-*i*]purin-5(4*H*)-one; (±)R-1-[(ϵ)-3[2-[phenylpyrazolo (1,5-a) pyridin-3-yl]acryloyl]-2-piperidine ethanol; 8-azaxanthines such as 7-cyclopentyl-1,3-dipropyl-8-azaxanthine; tetrahydrobenzothiophenones such as ethyl-3-(benzylthio)-4-oxo-4,5,6,7-tetrahydrobenzo[c]thiophene-1-carboxylate; N-6-cyclopentyl-3'-substituted xylo-furanosyl adenosines. *See* Van Calinbergh, *J. Med. Chem.* **40**, 3765 (1997).

Additional A_1 adenosine receptor (A_1AR) antagonists are set forth in U.S. Patent Application No. 08/753,048, filed November 19, 1996 (now U.S. Patent No. 5,786,360 to Neely, issued July 28, 1998), incorporated herein by reference in its entirety. Additional A_1AR antagonists useful in the practice of the present invention include those set forth in, for example, U.S. Patent Nos. 5,599,671 to Jacobson et al.; 5,998,387 to Belardinelli; 5,066,655, to Olsson; 5,298,508 to Jacobson et al.; 4,696,932 to Jacobson et al.; 5,773,530 to Akahane et al.; 5,565,566, to Olsson; 5,668,139 to Belardinelli et al.; 5,446,046 to Bellardinelli et al.; and 5,310,916 to Jacobson et al. (all of which are incorporated herein by reference).

Still other A_1AR antagonists useful in the practice of the present invention include those set forth in, for example, published PCT Applications WO 97/24363A1 to Belardinelli et al.; WO 95/11904A1 to Belardinelli et al.; and WO 88/08303A1 to Olsson; European Patent Application No. EP 764647 to Connell et al.; Australian Patent Application Nos. AU1044995A1, AU699630B2, and AU728439B2, all to Belardinelli et al.; Japanese applications JP8099976A to Shiokawa et al. and JP9216883A to Kuroda; and Chinese Application No. CN1206420A to Belardinelli et al. (all of which are incorporated herein by reference).

Additionally, selective analogs of adenosine receptor antagonists have been developed through the "functionalized congener" approach. Analogs of adenosine receptor ligands bearing functionalized chains have been synthesized and attached covalently to various organic moieties such as amines and peptides. Jacobson et

al., *J. Med. Chem.* **35**, 408 (1992) has proposed various derivatives of adenosine and theophylline for use as receptor antagonists.

Antibodies raised against the A_1 adenosine receptor that selectively target and bind to the receptor can also be used as A_1 adenosine receptor antagonists. Such antibodies targeted to the A_1 adenosine receptor can be produced routinely in accordance with well known methods of antibody production. As used herein, the term "A_1 adenosine receptor antagonist" encompasses antibodies that selectively or specifically bind to the receptor, when such antibodies are used for their antagonist effects. The term "antibody," as used herein, includes polyclonal antibodies, monoclonal antibodies, and active fragments or polypeptides thereof. Antibodies to the A_1AR are set forth in, for example El-Etr, *Neuro. Sci. Lett.* **145**, 15 (1992); Ku et al., *J. Immunol.* **139**, 2376 (1987); Salmon et al., *J. Immunol.* **151**, 2775 (1993); and US Patent No. 5,144,010 to Erlanger and Cleveland.

P_{2X} purinoceptor antagonists are also known in the art. An example of a selective P_{2X} purinoceptor antagonist is pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS). Additional specific pharmacological antagonists of purinoceptors have been described by Humphrey et al., *Naunyn-Schmied. Arch. Pharmacol.* **352**, 585 (1995); Abracchio and Burnstock, *Pharmacol. Ther.* **64**, 445 (1994); Bultmann et al., *Naunyn-Schmied. Arch. Pharmacol.* **354**, 481 (1996); and Bultmann et al., *Naunyn-Schmied. Arch. Pharmacol.* **354**, 498 (1996). Antibodies raised against the P_{2X} purinoceptor that selectively target and bind to this receptor can also be used as P_{2X} purinoceptor antagonists. Such antibodies targeted to the P_{2X} purinoceptor can be produced routinely in accordance with well known methods of antibody production. As used herein, the term " P_{2X} purinoceptor antagonist" encompasses antibodies that selectively or specifically bind to the receptor, when such antibodies are used for their antagonist effects. As set forth above, the term "antibody," as used herein, includes polyclonal antibodies, monoclonal antibodies, and active fragments or polypeptides thereof.

An active compound of the present invention may optionally be provided and administered in the form of a free base, or may be in the form of a pharmaceutically acceptable salt thereof. Suitable pharmaceutically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-

toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt and N,N´-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt.

The present invention provides methods of preventing and treating disorders of the immune system, wherein an effective amount of an A_1 adenosine receptor antagonist, and/or a P_{2X} purinoceptor antagonist, or a combination thereof, is administered to a subject in need of such treatment. A single compound that antagonizes both the A_1 adenosine receptor and the P_{2X} purinoceptor may also be used in the methods of the present invention.

By the terms "treating " or "treatment" of an immune system disorder, it is intended that the severity of the disorder or the symptoms of the disorder are reduced, or the disorder is partially or entirely eliminated, as compared to that which would occur in the absence of treatment. Treatment does not require the achievement of a complete cure of the disorder.

By the terms "preventing" or "prevention" of the immune system disorder, it is intended that the inventive methods eliminate or reduce the incidence or onset of the disorder, as compared to that which would occur in the absence of treatment. Alternatively stated, the present methods slow, delay, control, or decrease the likelihood or probability of the disorder in the subject, as compared to that which would occur in the absence of treatment.

An "effective amount" is that amount able to reduce the severity, development, or onset of the disorder that would occur in the absence of the antagonists, or slow the progress (over time) of the disorder, compared to that which would occur in the absence of said antagonists. The term "effective amount" also refers to a concentration of an A_1 adenosine receptor antagonist, P_{2X} purinoceptor antagonist, or combination thereof, which is sufficient to interfere with pathological changes caused by the disorder. Preferably, the A_1 adenosine receptor antagonist is a selective A_1 adenosine receptor antagonist. Also preferably, the P_{2X} purinoceptor antagonist is a selective P_{2X} purinoceptor antagonist.

The therapeutically effective dosage of any specific compound, the use of which is in the scope of the present invention, will vary somewhat from compound to

compound, patient to patient, and will depend upon the condition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 20 mg/kg body weight will have therapeutic efficacy, with still higher dosages potentially being employed for oral and/or aerosol administration. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, all weights being calculated based upon the weight of the active base, including the cases where salt is employed. Typically a dosage from about 0.56 mg/kg to about 5 mg/kg will be employed. In certain circumstances, higher or lower doses may be also appropriate. The daily dose can be administered either by a single dose in the form of an individual dosage unit or several smaller dosage units, by multiple administration of subdivided dosages at certain intervals, or by a continuous infusion.

The methods of the present invention may be carried out in conjunction with other therapies for the immune system disorder that is being treated or prevented. For example, pharmaceutical compositions known to be useful in the treatment of HIV infection and AIDS may be administered concurrently with the A_1 antagonists or P_{2X} purinoreceptor antagonists of the present invention. Alternatively, a course of treatment known to be useful in the treatment of HIV infection and AIDS may be carried out while a course of treatment utilizing the present invention is also carried out.

The present invention also provides pharmaceutical formulations, both for veterinary and for human medical use, which comprise the active compounds of the invention, together with one or more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof. Pharmaceutically acceptable carriers include, but are not limited to, saline, water, dextrose and water, cyclodextrins or similar sugar solutions, low dose sodium hydroxide solutions, propylene glycol, and polyethylene glycol.

The formulations of the present invention may be suitable for inhalation (*e.g.*, as an aerosol), oral, rectal, topical, nasal, ophthalmic, parenteral (including but not limited to subcutaneous, intramuscular, intravenous, and intraarterial), intraarticular, intrapleural, intraperitoneal, vaginal, bladder instillation, and intracerebral

(alternatively, into the cerebral spinal space) administration. Formulations suitable for oral, inhalation, and parenteral administration are preferred.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound as a powder or as granules; or a non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which is optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tables comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound, which is preferably isotonic with the blood of the recipient and pyrogen-free.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

In yet another aspect of the present invention, there is provided an injectable, stable, sterile composition comprising an active compound or compounds of the present invention, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for injection thereof into the subject. The unit dosage form typically comprises from

about 10 mg to about 10 grams of the compound or salt. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent which is physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidylcholine.

Further, the present invention provides liposomal formulations of the compounds of present invention. The technology for forming liposomal suspensions is well known in the art. When the compound is an aqueous-soluble salt, using conventional liposome technology, the same may be incorporated into lipid vesicles. In such an instance, due to the water solubility of the compound or salt, the compound or salt will be substantially entrained within the hydrophilic center or core of the liposomes. The lipid layer employed may be of any conventional composition and may either contain cholesterol or may be cholesterol-free. When the compound or salt of interest is water-insoluble, again employing conventional liposome formation technology, the salt may be substantially entrained within the hydrophobic lipid bilayer which forms the structure of the liposome. In either instance, the liposomes which are produced may be reduced in size, as through the use of standard sonication and homogenization techniques.

The following Examples are provided to illustrate the present invention, and should not be construed as limiting thereof. Examples 1 and 2 are carried out generally according to the methods set forth in Jackson et al., *J. Clin. Microbiol.* ***26,1416 (1988)***. Examples 3, 4, and 5 are carried out generally as set forth in Heredia, et al., *J Acquired Immune Deficiency Syndromes* **25**, 246 (2000); St. Clair, et al., *Science* **253**,1557 (1991); and Asin, et al., *J. Virol.* **73**, 3893 (1999)

EXAMPLE 1
Viral Culture Method for HIV-1: Isolation of PBMC From Normal (HIV-1 negative) Donors

PBMC are obtained from the buffy coats of whole-blood donors negative for HIV-1 antibodies. Each buffy coat is diluted 1:3 with sterile phosphate-buffered saline (pH 7.3 at 24° C) within eight hours of donation. Thirty milliliters of diluted buffy coat is layered over 15 ml of sterile Ficoll-Paque (Pharmacia, Inc., Piscataway, N. J.) and centrifuged at 350 x *g* for 30 to 45 minutes at room temperature. The layer containing the PBMC is removed and washed twice in sterile phosphate-

buffered saline. Pelleted cells are suspended and pooled in stimulation medium (fresh RPMI 1640 medium) [GIBCO Laboratories, Grand Island, N.Y.] containing 20% heat-inactivated fetal bovine serum (FBS) [GIBCO], two mM glutamine, four μg of Polybrene [Sigma Chemical Co., St. Louis, Mo.] per ml, 200 U of penicillin per ml, 200 μg of streptomycin per ml, and four μg of phytohemagglutinin-P [Sigma] per ml) and placed in upright 275-ml tissue culture flasks at a concentration of 10^6 cells per ml. After two to four days in culture at 37° C in a 5% CO_2 atmosphere, the supernatant above the settled cells is removed to bring the volume to one-fourth that of the original. Unwashed samples of 5×10^6 or 3×10^6 of these donor PBMCs are used to feed cultures of PBMCs from patients HIV-1 antibody positive.

EXAMPLE 2

Viral Culture Method for HIV-1: Isolation Of PBMC From Blood Of HIV-Antibody Positive Patients

PBMC are obtained from whole-blood of patients positive for HIV-1 antibodies. For separation of PBMC from patients, 20 to 30 ml of heparinized blood is diluted 1:3 with sterile phosphate-buffered saline within 24 h collection. Thirty-milliliter portions of diluted blood are layered over 15 ml of sterile Ficoll-Paque and centrifuged at 350 x *g* for 30 to 45 min at room temperature. The layer containing the PBMC is removed and washed twice in sterile phosphate-buffered saline. Pelleted cells are suspended and pooled in 10 ml of T-cell growth factor medium (fresh RPMI 1640 medium containing 20% heat-inactivated FBS, 5% interleukin-2 (IL-2) [Cellular Products, Buffalo, N.Y.], 2 mM glutamine, 5 μg of Polybrene per ml, 200 U of penicillin per ml, and 200 μg of streptomycin per ml).

PBMCs from normal (HIV-1 negative) subjects are stimulated with 2.5 mg/ml phytohemagglutinin-P (PHA) (Boehringer Mannheim, Indianapolis, IN) for three days. A cell suspension volume equal to 10^7 PBMC from HIV-antibody positive patients is placed in an upright 50-ml flask along with 5×10^6 PHA-stimulated donor PBMC. The final cell suspension volume is diluted to 15 ml with T-cell growth factor medium. These co-cultures are incubated at 37°C in a 5% CO_2 atmosphere for as long as 28 days. Approximately seven ml of culture medium above the settled cells is removed every three to four days for HIV-1 p24 antigen detection and replaced with an equal volume of fresh T-cell growth factor medium. An additional 3×10^6 PHA-stimulated donor PBMC are added every seven days.

EXAMPLE 3

Effect Of A_1 Adenosin Receptor Antagonist, P_{2X} Purinoceptor Antagonist, And A_1 Adenosine Receptor Antagonist Plus A P_{2X} Purinoceptor Antagonist On HIV-1 Replication

PHA-stimulated donor PMBCs (10^7) are sedimented by low speed centrifugation and resuspended in 10 ml infective cell-free supernatant from cell cultures of PBMCs from HIV-antibody positive patients co-cultured with PBMCs from normal subjects containing 360 ng of p24/ml for two hours. Mock-infected cells are used as controls. PBMCs are then washed three times with PBS and cultured in 5% CO_2 at 37° C, in RPMI-1640/10% FBS supplemented with 10 U/ml IL-2. PBMCs are seeded in 96-well flat-bottom plates at a density of 2 x 10^5 PBMCs/200 µl. Mock-infected cells are treated with IL-2 alone. Infected PBMCs are treated with ***(1)*** IL-2 alone (controls), ***(2)*** an A_1 adenosine receptor antagonist (L-97-1, 1 nM – 10 µM), ***(3)*** a P_{2X} purinoceptor antagonist, such as pyridoxalphosphate-6-azophenyl-2',4' disulfonic acid (PPADS) (5 – 50 µM), or ***(4)*** L-97-1 (1 nM – 10 µM) plus PPADS (5 – 50 µM). Following three days of culture, one half of the medium is replaced with fresh medium containing IL-2 alone (mock-infected and controls) or IL-2 plus treatments for infected cells. After ten days of culture, HIV-1 p24 antigen production in the cell culture supernatant is assayed. Experiments for mock-infected cells and infected cells for controls (IL-2 alone) and for each treatment (L-97-1, PPADS, or L-97-1 plus PPADS) are performed with three different batches of cells and two serial supernatants are assayed for HIV p24 antigen in duplicate.

EXAMPLE 4

Detection of HIV antigen

Culture supernatant fluids are tested for the presence of p24 core antigen of HIV with the use of an enzyme-linked immunosorbent assay (Abbott Laboratories, North Chicago, Ill.) Culture supernatants are removed every three to four days and frozen in a one-mL aliquots at -20 °C. Specimens are thawed within one month of collection and tested according to the manufacturers directions.

EXAMPLE 5
Analysis of Data

Statistical analysis of the data is performed with the use of the Student's *t* test for unpaired data for each concentration of L-97-1, PPADS, or L-97-1 plus PPADS (treatment) versus control (IL-2 alone). $P < 0.05$ is accepted as statistically significant.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

```
* * * * * * * * * *  Welcome to STN International  * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS  4  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS  5  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS  6  SEP 21  CA/CAplus fields enhanced with simultaneous left and right
                  truncation
 NEWS  7  SEP 25  CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS  8  SEP 25  CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS  9  SEP 25  CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 10  SEP 28  CEABA-VTB classification code fields reloaded with new
                  classification scheme
 NEWS 11  OCT 19  LOGOFF HOLD duration extended to 120 minutes
 NEWS 12  OCT 19  E-mail format enhanced
 NEWS 13  OCT 23  Option to turn off MARPAT highlighting enhancements available
 NEWS 14  OCT 23  CAS Registry Number crossover limit increased to 300,000 in
                  multiple databases
 NEWS 15  OCT 23  The Derwent World Patents Index suite of databases on STN
                  has been enhanced and reloaded
 NEWS 16  OCT 30  CHEMLIST enhanced with new search and display field
 NEWS 17  NOV 03  JAPIO enhanced with IPC 8 features and functionality
 NEWS 18  NOV 10  CA/CAplus F-Term thesaurus enhanced
 NEWS 19  NOV 10  STN Express with Discover! free maintenance release Version
                  8.01c now available
 NEWS 20  NOV 20  CAS Registry Number crossover limit increased to 300,000 in
                  additional databases
 NEWS 21  NOV 20  CA/CAplus to MARPAT accession number crossover limit increased
                  to 50,000
 NEWS 22  DEC 01  CAS REGISTRY updated with new ambiguity codes
 NEWS 23  DEC 11  CAS REGISTRY chemical nomenclature enhanced
 NEWS 24  DEC 14  WPIDS/WPINDEX/WPIX manual codes updated
 NEWS 25  DEC 14  GBFULL and FRFULL enhanced with IPC 8 features and
                  functionality
 NEWS 26  DEC 18  CA/CAplus pre-1967 chemical substance index entries enhanced
                  with preparation role
 NEWS 27  DEC 18  CA/CAplus patent kind codes updated
 NEWS 28  DEC 18  MARPAT to CA/CAplus accession number crossover limit increased
                  to 50,000
 NEWS 29  DEC 18  MEDLINE updated in preparation for 2007 reload
 NEWS 30  DEC 27  CA/CAplus enhanced with more pre-1907 records

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Jan 2007 (20070104/PD)
FILE LAST UPDATED: 4 Jan 2007 (20070104/ED)
HIGHEST GRANTED PATENT NUMBER: US7159245
HIGHEST APPLICATION PUBLICATION NUMBER: US2007006355
CA INDEXING IS CURRENT THROUGH 4 Jan 2007 (20070104/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Jan 2007 (20070104/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

=> e wilson constance n/in
E1 1 WILSON CONAN EDWARD/IN
E2 2 WILSON CONSTANCE A/IN
E3 3 --> WILSON CONSTANCE N/IN
E4 3 WILSON CONSTANCE NEELY/IN
E5 1 WILSON COREY/IN
E6 4 WILSON CRAIG/IN
E7 15 WILSON CRAIG A/IN
E8 1 WILSON CRAIG B/IN
E9 2 WILSON CRAIG DOUGLAS/IN
E10 1 WILSON CRAIG L/IN
E11 6 WILSON CRAIG M/IN
E12 2 WILSON CRAIG MURRAY MANSELL/IN

=> s e4
L1 3 "WILSON CONSTANCE NEELY"/IN

=> d l1,cbib,1-3

L1 ANSWER 1 OF 3 USPATFULL on STN
2005:138608 A1 adenosine receptor antagonists.
Wilson, Constance Neely, Research Triangle Park, NC, UNITED STATES
Partridge, John J., Chapel Hill, NC, UNITED STATES
US 2005119258 A1 20050602
APPLICATION: US 2004-780296 A1 20040217 (10)
PRIORITY: US 2003-448212P 20030219 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 2 OF 3 USPATFULL on STN
2004:158607 Methods and formulations for increasing the affinity of a1 adenosine receptor ligands for the a1 adenosine receptor.
Wilson, Constance Neely, Raleigh, NC, UNITED STATES
US 2004121406 A1 20040624
APPLICATION: US 2003-475925 A1 20031024 (10)
WO 2002-US16218 20020523
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L1 ANSWER 3 OF 3 USPATFULL on STN
2004:145101 Methods and formulations of using A1 adenosine receptor antagonists and P2x purinoceptor antagonists for the treatment and prevention of immune system disorders.
Wilson, Constance Neely, Raleigh, NC, UNITED STATES
US 2004110774 A1 20040610
APPLICATION: US 2003-713860 A1 20031117 (10)
PRIORITY: US 2001-292072P 20010518 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l1,cbib,clm,1-3

L1 ANSWER 1 OF 3 USPATFULL on STN
2005:138608 A1 adenosine receptor antagonists.
Wilson, Constance Neely, Research Triangle Park, NC, UNITED STATES
Partridge, John J., Chapel Hill, NC, UNITED STATES
US 2005119258 A1 20050602
APPLICATION: US 2004-780296 A1 20040217 (10)
PRIORITY: US 2003-448212P 20030219 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of formula (1): ##STR30## wherein: A is a 5- or 6-membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms

selected from the group consisting of N, O, and S; R_2 is of the formula (i): $(CH_2)_{r-A'}-R_4$ (i) wherein: A' is a 5- or 6-membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms selected from the group consisting of N, O, and S; r is an integer ranging from 1 to 20; R_4 is selected from the group consisting of H; NH_2; $(CH_2)_{sOH}$, wherein s is an integer ranging from 1 to 8; R_{14COOH}, wherein R_{14} is an alkyl or alkylidene group having 1 to 8 carbon atoms, halo, NHR_8, NR_{8R9}, $NHCOR_8$, NR_{8COR9}, SO_{3H} and PO_{3H2}; R_3 is selected from the group consisting of H, NH_2, R_{15COOH}, wherein R_{15} is an alkyl or alkylidene group having 1 to 8 carbon atoms, and $(CH_2)_{tOH}$, wherein t is an integer ranging from 1 to 8; halo, NHR_8, NR_{8R9}, $NHCOR_8$, NR_{8COR9}, SO_{3H} and PO_{3H2}; q is an integer ranging from 1 to 8; or R_1 or R_2 is a C_{1-C8} alkanyl group, C_{2-C8}-alkenyl- or C_{2-C8}-alkynyl-group which is optionally substituted by --CN, $--CH_{2NR6R7OH}$, $--OR_8$, $--NR_{6R7}$, $--NHCOR_8$, $--NHCONR_{6R7}$, halogen, $--OCOR_8$, $--OCH_{2COOH}$, $--OCH_{2COOR8}$, $--SO_{2R5}$, --S--R_5, --NHCONH phenyl, $--OCH_{2}$--$_{CONR6R7}$, $--OCH_{2CH2OH}$, $--SO_{2}$--$_{CH2}$--$_{CH2}$--$_{O}$--$_{COR8}$, $--OCH_{2}$--$_{CH2}$--$_{NR6R7}$, $--SO_{2}$--$_{CH2}$--$_{CH2}$--OH, $--CONHSO_{2R8}$, $--CH_{2CONHSO2R8}$, $--OCH_{2CH2OR8}$, --COOH, $--COOR_8$, $--CONR_{6R7}$, --CHO, $--SR_8$, $--SOR_{8}$--$_{SO2R8}$, $--SO_{3H}$, $--PO_{3H2}$, $--SO_{2NR6R7}$, $--OCH_{2}$--$_{CH2OCOR8}$, --CH.dbd.NOH, --CH.dbd.NOR_8, --COR_9, $--CH(OH)R_9$, $--CH(OR_8)_2$, --CH.dbd.CH--R_{10}, $--OCONR_{6R7}$, ##STR31## or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted by methyl; or denotes phenyl-C_{1-C6}-alkylene, phenyl-C_{2-C6}-alkenylene or phenyl-C_{2-C6}-alkynylene, in which the phenyl ring is optionally substituted, either directly or via a C_{1-C4}-alkylene group, with one or more of the following groups: $--C_{1-C3}$-alkyl, --CN, $--CH_{2NR6R7}$, $--NO_2$, --OH, $--OR_8$, $--CH_{2}$--$_{NH}$--$_{SO2}$--$_{R8}$, $--NHCOR_8$, $--NHCONR_{6R7}$, halogen, $--OCOR_8$, $--OCH_{2COOH}$, $--OCH_{2COOR8}$, $--CH_{2OCOR8}$, $--SO_{2R5}$, $--OCH_{2}$--$_{CONR6R7}$, $--OCH_{2CH2OH}$, $--OCH_{2}$--$_{CH2}$--$_{NR6R7}$, $--CONHSO_{2R8}$, $--OCH_{2CH2OR8}$, --COOH, $--COOR_8$, $--CF_3$, cyclopropyl, $--CONR_{6R7}$, $--CH_{2OH}$, $--CH_{2OR8}$, --CHO, $--SR_8$, $--SOR_8$, $--SO_{2R8}$, $--SO_{3H}$, $--PO_{3H2}$, $--SO_{2NR6R7}$, $--OCH_{2}$--$_{CH2OCOR8}$, --CH.dbd.NOH, --CH.dbd.NOR_8, --COR_9, $--CH(OH)R_9$, $--CH(OR_8)_2$, $--NHCOOR_8$, $--CH_{2CONHSO2R8}$, --CH.dbd.CH--R_{10}, $--OCONR_{6R7}$, $--CH_{2}$--$_{O}$--$_{CONR6R7}$, $--CH_{2}$--$_{CH2}$--$_{O}$--$_{CONR6R7}$, ##STR32## or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted by methyl; or denotes C_{3-C7}-cycloalkyl-C_{1-C6}-alkylene-, C_{3-C7}-cycloalkyl-C2-C6-alkenylene-, C_{3-C7}-cycloalkyl-C_{2-C6}-alkynylene-, in which the cycloalkyl group may optionally be substituted, either directly or via a C_{1-4}-alkylene group, by --CN, $--CH_{2NR6R7}$, =O, --OH, $--OR_8$, $--NR_{6R7}$, $--NHCOR_8$, $--NHCONR_{6R7}$, halogen, $--OCOR_8$, $--OCH_{2COOH}$, $--OCH_{2COOR8}$, $--CH_{2OCOR8}$, $--SO_{2R5}$, $--OCH_{2CONR6R7}$, $--OCH_{2CH2OH}$, $--OCH_{7}$--$_{CH2}$--$_{NR6R7}$, $--OCH_{2CH2OR8}$, --COOH, $--COOR_8$, $--CONR6R_7$, $--CH_{2OH}$, $--CH_{2OR8}$, --CHO, $--SR_8$, $--SOR_8$, $--SO_{2R8}$, $--SO_{3H}$, $--PO_{3H2}$, $--SO_{2NR6R7}$, $--OCH_{2}$--$_{CH2}$--$_{O}$--$_{COR8}$, --CH.dbd.NOH, --CH.dbd.NOR9, --COR_9, $--CH(OH)R_9$, $--CONHSO_{2R8}$, $--CH(OR_8)_2$, $--NHCOOR_8$, --CH.dbd.CH--R_{10}, $--OCONR_{6R7}$, $--CH_{2}$--$_{O}$--$_{CONR6R77}$, $--CH_{2}$--$_{CH2}$--$_{O}$--$_{CONR6R7}$, ##STR33## or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted by methyl; or denotes a group of the formula A-CI--$C_{6-alkylene}$-, A-CONH--$C_{1-C6-alkylene}$-, A-CONH--$C_{2-C6-alkenylene}$-, A-CONH--$C_{2-C6-alkynylene}$-

, A-NH--CO--$C_{1-C6-alkylene}$, A-NH--CO--C_{2-C6-}
alkenylene, A-NH--CO--C_{2-C6} alkynylene, A-C_{2-C6-}
alkenylene- or A-$C_{2-C6-alkynylene}$, wherein A is a C- or
N-linked 5- or 6-membered heterocyclic ring, 5- or 6-membered aromatic
ring, or 5-or 6-membered heteroaromatic ring which contains nitrogen,
oxygen or sulphur as heteroatoms and may optionally be mono- or
polysubstituted, by $C_{1-C4-alkyl}$, halogen, --OR_8, --CN,
--NO_2, --NH_2, --CH_{2NR6R7}, --OH, .dbd.O, a
ketal, --COOH, --SO_{3H}, --PO_{3H2}, --$COOR_8$,
--$CONR_{6R7}$, --COR_9, --SO_{2--R8},
--$CONR_{6R7}$ or ##STR34## R_5 denotes
$C_{1-C4-alkyl}$, optionally substituted by OH, $OCOR_8$,
NH_2, NR_{6R7} or $NHCOR_8$, R_6 denotes hydrogen, an
optionally substituted $C_{3-6-cycloalkyl}$ group, a branched or
ulibranched alkyl-, alkenyl- or alkynyl group having up to 10 carbon
atoms, preferably a $C_{1-C4-alkyl}$ group, which may optionally be
substituted by hydroxy, phenyl, substituted phenyl, amino, substituted
amino, C_1 to C_8, or it denotes --$(CH_2)_{m--}$
$NHCOOR_8$ wherein m=1, 2, 3 or 4; R_7 denotes hydrogen, an
optionally substituted $C_{3-6-cycloalkyl}$ group, a branched or
unbranched alkyl-, alkenyl- or alkynyl group having up to 10 carbon
atoms, which may optionally be substituted by hydroxy, phenyl,
substituted phenyl, amino, substituted amino, C_1 to C_8, -or it
denotes --$(CH_2)_{m--NHCOOR8}$ wherein m=1, 2, 3 or 4; or
R_6 and R_7 together with the nitrogen atom form a saturated or
unsaturated 5- or 6-membered ring which may contain as heteroatoms
nitrogen, oxygen or sulphur, while the heterocyclic ring may be
substituted by a branched or unbranched $C_{1-4-alkyl}$ group, or may
carry one of the following groups: --$(CH_2)_{n--NH2}$, .dbd.O,
a ketal-preferably --O--$CH_{2--CH2--O--}$, --$(CH_2)_n$.NH--
$C_{1-C4-alkyl}$, --$(CH_2)_{n--N}(C_{1-C8-alkyl})$,
--$(CH_2)_{n--NHCOOR8}$, (n=2, 3, 4), halogen, --OR_8,
--CN, --NO_2, --NH_2, --CH_{2NR6R7}, --OH, --COOH,
--SO_{3H}, --PO_{3H2}, --$COOR_8$, --$CONR_{6R7}$,
--SO_{2R8}, R_8 denotes hydrogen, $C_{1-C8-alkyl}$ or
$C_{2-C8-alkenyl}$ or $C_{2-C8-alkynyl}$ optionally
substituted with CO_{2H}, a benzyl- or phenyl-group, which is
optionally mono- or polysubstituted by OCH_3; R_9 denotes
$C_{1-C8-alkyl}$ or $C_{2-C8-alkenyl}$ or $C_{2-Cs-alkynyl}$
optionally substituted with CO_{2H}, optionally substituted phenyl,
optionally substituted benzyl, $C_{3-C6-cycloalkyl}$, and R_{10}
denotes --$COOR_8$, --CH_{2OR8}, --$CONR_{6R7}$, hydrogen,
$C_{1-C3-alkyl}$, optionally substituted phenyl,
--CH_{2NR6R7}; and pharmaceutically acceptable salts,
hydrates and prodrugs thereof.

2. The compound of claim 1, wherein at least one of R_3 and R_4
is independently selected from the group consisting of SO_{3H} and
PO_{3H2}.

3. The compound of claim 1, wherein R_1 or R_2 is a
C_{1-C8} alkanyl group, $C_{2-C8-alkenyl}$ group or
C_{2-C8} alkynyl group which is optionally substituted by
NR_{6R7}, --SO_{3H}, or --PO_{3H2}.

4. The compound of claim 1, wherein A is phenyl.

5. The compound of claim 1, wherein A' is phenyl.

6. The compound of claim 1, wherein: R_1 is a C_{1-C8}
alkanyl group, $C_{2-C8-alkenyl}$ group or C_{2-C8} alkynyl
group which is optionally substituted by NR_{6R7} or --SO_{3H};
A is phenyl; and A' is phenyl.

7. The compound of claim 6, wherein at least one of R_3 and R_4
is independently selected from the group consisting of SO_{3H} and
PO_{3H2}.

8 The compound of claim 1, wherein said compound is selected from the
group consisting of: 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-
propylxanthine; 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(3-
pyridyl)methyl]xanthine; 3-[2-(4-Aminophenyl)ethyl]--propyl-8-[(4-

thiazolyl)methyl]xanthine; 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-dimethylamino)propylxanthine; 3-[2-[4-(6-Aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propylxanthine; 8-Benzyl-1-propyl-3-[4-(4-sulfonoxyphenyl)butyl]xanthine; 8-Benzyl-1-propyl-3-[2-(4-sulfonoxyphenyl)ethyl]xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine; and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

9. The compound of claim 1, wherein said compound is selected from the group consisting of: 8-Benzyl-1-propyl-3-[4-(4-sulfonoxyphenyl)butyl]xanthine; 8-Benzyl-1-propyl-3-[2-(4-sulfonoxyphenyl)ethyl]xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-(4-fluorobenzyl)-1-propylxanthine; 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(thiophen-2-yl)methyl]xanthine; 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(1H-tetrazol-5-yl)methyl]xanthine; 8-(2-Acetaminobenzyl)-3-[2-(4-aminophenyl)ethyl]-1-propylxanthine; 8-(2-Aminobenzyl)-3-(2-phenylethyl)-1-propylxanthine; 8-Benzyl-3-[2-(3-carboxyphenyl)ethyl]-1-propylxanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(8-sulfonoxyoctyl)xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(5-sulfonoxypentyl)xanthine; and phammaceutically acceptable salts, hydrates and prodrugs thereof.

10. The compound of claim 1, wherein said compound is selected from the group consisting of: 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-propylxanthine; 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine; 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine; 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-dimethylamino)propylxanthine; 3-[2-[4-(6-Aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propyl xanthine; and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

11. The compound of claim 1, wherein said compound is selected from the group consisting of: 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(5-sulfonoxypentyl)xanthine; and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

12. A composition comprising a compound of claim 1 in a pharmaceutically acceptable carrier.

L1 ANSWER 2 OF 3 USPATFULL on STN
2004:158607 Methods and formulations for increasing the affinity of a1 adenosine receptor ligands for the a1 adenosine receptor.
Wilson, Constance Neely, Raleigh, NC, UNITED STATES
US 2004121406 A1 20040624
APPLICATION: US 2003-475925 A1 20031024 (10)
WO 2002-US16218 20020523
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of increasing the affinity of an A_1 adenosine receptor (A_{1AR}) ligand for an A_1 adenosine receptor comprising: contacting an A_1 adenosine receptor ligand with a glycolipid or an analog thereof; and binding the contacted A_1 adenosine receptor ligand with an A_1 adenosine receptor.

2. The method according to claim 1, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor antagonist.

3. The method according to claim 1, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor agonist.

4. The method according to claim 1, wherein the A_1 adenosine receptor ligand is an antibody specific for the A_1 adenosine receptor.

5. The method according to claim 4, wherein the antibody is a monoclonal antibody.

6. The method according to claim 1, wherein the A_1 adenosine

receptor ligand is an endotoxin.

7. The method according to claim 6, wherein the endotoxin is lipopolysaccharide (LPS)

8. The method according to claim 1, wherein the glycolipid is selected from the group consisting of monosialoganglioside, lactocerebroside, and galactocerebroside, NBD-galactocerebroside, and mixtures thereof.

9. The method according to claim 1, wherein the A_1 adenosine receptor is in a membrane.

10. The method according to claim 1, wherein the A_1 adenosine receptor is purified A_1 adenosine receptor protein.

11. The method according to claim 1, wherein the A_1 adenosine receptor is a polypeptide that is synthesized based on an amino acid sequence of a ligand binding site for the A_{1AR} protein.

12. The method according to claim 1, wherein the glycolipid or analog thereof is chemically linked to the A_1 adenosine receptor ligand.

13. The method according to claim 1, wherein the glycolipid or analog thereof is conjugated to the A_1 adenosine receptor ligand.

14. The method according to claim 1, wherein the glycolipid or analog thereof is formulated in a liposome with the A_1 adenosine receptor ligand.

15. A method of increasing the affinity of an A_1 adenosine receptor (A_{1AR}) ligand for an A_1 adenosine receptor comprising:
contacting an A_1 adenosine receptor with a glycolipid or an analog thereof; and binding the contacted A_1 adenosine receptor with an A_1 adenosine receptor ligand.

16. The method according to claim 15, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor antagonist.

17. The method according to claim 15, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor agonist.

18. The method according to claim 15, wherein the A_1 adenosine receptor ligand is an antibody specific for the A_1 adenosine receptor.

19. The method according to claim 18, wherein the antibody is a monoclonal antibody.

20. The method according to claim 15, wherein the A_1 adenosine receptor ligand is an endotoxin.

21. The method according to claim 20, wherein the endotoxin is lipopolysaccharide (LPS).

22. The method according to claim 15, wherein the glycolipid is selected from the group consisting of monosialoganglioside, lactocerebroside, and galactocerebroside, NBD-galactocerebroside, and mixtures thereof.

23. The method according to claim 15, wherein the A_1 adenosine receptor is in a membrane.

24. The method according to claim 15, wherein the A_1 adenosine receptor is purified A_1 adenosine receptor protein.

25. The method according to claim 15, wherein the A_1 adenosine receptor is a polypeptide that is synthesized based on an amino acid sequence of a ligand binding site for the A_{1AR} protein.

26. The method according to claim 15, wherein the glycolipid or analog thereof is chemically linked to the A_1 adenosine receptor ligand.

27. The method according to claim 15, wherein the glycolipid or analog thereof is conjugated to the A_1 adenosine receptor ligand.

28. The method according to claim 15, wherein the glycolipid or analog thereof is formulated in a liposome with the A_1 adenosine receptor ligand.

29. A method of increasing the affinity of an A_1 adenosine receptor ligand for an A_1 adenosine receptor, comprising concurrently contacting an A_1 adenosine receptor, an A_1 adenosine receptor ligand, and a glycolipid or analog thereof.

30. The method according to claim 29, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor antagonist.

31. The method according to claim 29, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor agonist.

32. The method according to claim 29, wherein the A_1 adenosine receptor ligand is an antibody specific for the A_1 adenosine receptor.

33. The method according to claim 32, wherein the antibody is a monoclonal antibody.

34. The method according to claim 29, wherein the A_1 adenosine receptor ligand is an endotoxin.

35. The method according to claim 34, wherein the endotoxin is lipopolysaccharide (LPS).

36. The method according to claim 29, wherein the glycolipid is selected from the group consisting of monosialoganglioside, lactocerebroside, and galactocerebroside, NBD-galactocerebroside, and mixtures thereof.

37. The method according to claim 29, wherein the A_1 adenosine receptor is in a membrane.

38. The method according to claim 29, wherein the A_1 adenosine receptor is purified A_1 adenosine receptor protein.

39. The method according to claim 29, wherein the A_1 adenosine receptor is a polypeptide that is synthesized based on an amino acid sequence of a ligand binding site for the A_{1AR} protein.

40. The method according to claim 29, wherein the glycolipid or analog thereof is chemically linked to the A_1 adenosine receptor ligand.

41. The method according to claim 29, wherein the glycolipid or analog thereof is conjugated to the A_1 adenosine receptor ligand.

42. The method according to claim 29, wherein the glycolipid or analog thereof is formulated in a liposome with the A_1 adenosine receptor ligand.

43. In a method of delivering an A_1 adenosine receptor ligand to an A_1 adenosine receptor for the purpose of carrying out a diagnostic test, the improvement consisting of increasing the affinity of an A_1 adenosine receptor ligand for the A_1 adenosine receptor by: contacting an A_1 adenosine receptor ligand with a glycolipid or an analog thereof; and binding the contacted A_1 adenosine receptor ligand with an A_1 adenosine receptor.

44. The method of claim 43, wherein the A_1 adenosine receptor is present in a cell or cell membrane.

45. The method of claim 43, wherein the A_1 adenosine receptor is purified A_1 adenosine receptor protein.

46. The method of claim 43, wherein the contacting step comprises chemically linking the A_{1AR} ligand and the glycoplipid or analog thereof.

47. In a method of delivering an A_1 adenosine receptor ligand to an A_1 adenosine receptor for the purpose of carrying out a diagnostic

test, the improvement consisting of increasing the affinity of an A_1 adenosine receptor ligand for the A_1 adenosine receptor by: contacting an A_1 adenosine receptor with a glycolipid or an analog thereof; and binding the contacted A_1 adenosine receptor with an A_1 adenosine receptor ligand.

48. The method of claim 47, wherein the A_1 adenosine receptor is in a cell or cell membrane.

49. The method of claim 47, wherein the A_1 adenosine receptor is purified A_1 adenosine receptor protein.

50. In a method of administering an A_{1AR} ligand to a subject in need of such treatment, the improvement consisting of increasing the affinity of an A_{1AR} ligand for the A_{1AR} by administering to the subject the A_{1AR} ligand with a glycolipid or an analog thereof.

51. The method of claim 50, wherein the contacting step comprises chemically linking the A_{1AR} ligand and the glycolipid or analog thereof.

52. In a method of administering an A_{1AR} ligand to a subject in need of such treatment, the improvement consisting of increasing the affinity of an A_{1AR} ligand for the A_{1AR} by administering to the subject a glycolipid or an analog thereof and administering an A_{1AR} ligand.

53. A pharmaceutical formulation comprising: an A_1 adenosine receptor ligand; a glycolipid or glycolipid analog in an amount sufficient to enhance binding of the A_1 adenosine receptor ligand for the A_1 adenosine receptor; and a pharmaceutically acceptable carrier.

54. The formulation of claim 53, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor antagonist.

55. The formulation of claim 53, wherein the A_1 adenosine receptor ligand is an A_1 adenosine receptor agonist.

56. The method of claim 53, wherein the formulation is a liposomal formulation.

57. A method of increasing the affinity of an A_1 adenosine receptor (A_{1AR}) ligand for a binding site polypeptide of an A_1 adenosine receptor comprising: contacting an A_1 adenosine receptor ligand with a glycolipid or an analog thereof; and binding the contacted A_1 adenosine receptor ligand with a binding site polypeptide of an A_1 adenosine receptor.

58. The method of claim 57, wherein the binding site polypeptide is a polypeptide that is synthesized based on an amino acid sequence of a ligand binding site for the A_{1AR} protein.

59. The method of claim 57, wherein the binding site polypeptide is a purified binding site polypeptide.

60. A method of increasing the affinity of an A_1 adenosine receptor (A_{1AR}) ligand for a binding site polypeptide of an A_1 adenosine receptor comprising: contacting a binding site polypeptide of an A_1 adenosine receptor with a glycolipid or an analog thereof; and binding the contacted binding site polypeptide of an A_1 adenosine receptor with an A_1 adenosine receptor ligand.

61. The method of claim 60, wherein the binding site polypeptide is a polypeptide that is synthesized based on an amino acid sequence of a ligand binding site for the A_{1AR} protein.

62. The method of claim 60, wherein the binding site polypeptide is a purified binding site polypeptide.

L1 ANSWER 3 OF 3 USPATFULL on STN
2004:145101 Methods and formulations of using A1 adenosine receptor antagonists

and P2x purinoceptor antagonists for the treatment and prevention of immune system disorders.

Wilson, Constance Neely, Raleigh, NC, UNITED STATES

US 2004110774 A1 20040610
APPLICATION: US 2003-713860 A1 20031117 (10)
PRIORITY: US 2001-292072P 20010518 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A method for treating an immune system disorder in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of: (a) A_1 adenosine receptor antagonists; (b) P_{2X} purinoceptor antagonists; and (c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist; wherein said compound is administered in an amount effective to treat the immune system disorder.

2. The method of claim 1 wherein the disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

3. A method according to claim 1, wherein the A_1 adenosine receptor antagonist is an antibody that binds the A_1 adenosine receptor.

4. A method according to claim 1, wherein the P_{2X} purinoceptor antagonist is an antibody that binds the P_{2X} purinoceptor.

5. A method for preventing or delaying the onset of an immune system disorder in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of: (a) A_1 adenosine receptor antagonists; (b) P_{2X} purinoceptor antagonists; and (c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist; wherein said compound is administered in an amount effective to prevent or delay the onset of the immune system disorder that would occur in the absence of the administration.

6. The method of claim 5 wherein the disorder is selected from the group consisting of HIV infection, AIDS, and adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

7. The method according to claim 5, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

8. A method according to claim 5, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

9. A method for treating HIV infection or AIDS in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of: (a) A_1 adenosine receptor antagonists; (b) P_{2X} purinoceptor antagonists; and (c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist; wherein said compound is administered in an amount effective to treat the HIV infection or AIDS.

10. The method of claim 9, wherein the treatment is carried out in conjunction with another treatment for HIV infection or AIDS.

11. A method according to claim 9, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

12. A method according to claim 9, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

13. A method for preventing or delaying the onset of HIV infection or AIDS in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of: (a) A_1 adenosine receptor antagonists; (b) P_{2X} purinoceptor antagonists; and (c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist; wherein said compound is administered in an amount effective to prevent

or delay the onset of the HIV infection or AIDS that would occur in the absence of the administration.

14. A method according to claim 13, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

15. A method according to claim 13, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

16. A method for treating adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of: (a) A_1 adenosine receptor antagonists; (b) P_{2X} purinoceptor antagonists; and (c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist; wherein said compound is administered in an amount effective to treat adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

17. The method of claim 16, wherein the treatment is carried out in conjunction with another treatment for adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID).

18. A method according to claim 16, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

19. A method according to claim 16, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

20. A method for preventing or delaying the onset of adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject in need of such treatment, comprising administering to said subject a compound selected from the group consisting of: (a) A_1 adenosine receptor antagonists; (b) P_{2X} purinoceptor antagonists; and (c) a combination of at least one A_1 adenosine receptor antagonist and at least one P_{2X} purinoceptor antagonist; wherein said compound is administered in an amount effective to prevent or delay the onset of the adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) that would occur in the absence of the administration.

21. A method according to claim 20, wherein the A_1 adenosine receptor antagonist is an antibody that binds to the A_1 adenosine receptor.

22. A method according to claim 20, wherein the P_{2X} purinoceptor antagonist is an antibody that binds to the P_{2X} purinoceptor.

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf

>>> FOR DETAILS ON THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX
PLEASE SEE
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

```
=> e wilson c n/in
E1          17     WILSON C M/IN
E2           2     WILSON C M M/IN
E3          19 --> WILSON C N/IN
E4           1     WILSON C N R/IN
E5           2     WILSON C O/IN
E6           1     WILSON C O D O C/IN
E7           1     WILSON C O G/IN
E8          18     WILSON C P/IN
E9          74     WILSON C R/IN
E10          3     WILSON C R D/IN
E11         24     WILSON C S/IN
E12          4     WILSON C T/IN

=> s e3
L2          19 "WILSON C N"/IN

=> s l2 and (adenosine receptor? or P2? receptor? or P2? purinoceptors)
          7133 ADENOSINE
         61380 RECEPTOR?
           622 ADENOSINE RECEPTOR?
                 (ADENOSINE(W)RECEPTOR?)
         38861 P2?
         61380 RECEPTOR?
           219 P2? RECEPTOR?
                 (P2?(W)RECEPTOR?)
         38861 P2?
             5 PURINOCEPTORS
             4 P2? PURINOCEPTORS
                 (P2?(W)PURINOCEPTORS)
L3           8 L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEPTOR
               S)

=> d l3,bib,1-8

L3   ANSWER 1 OF 8  WPIDS COPYRIGHT 2007       THE THOMSON CORP on STN
Full Text
AN   2005-242392 [25]   WPIDS
DNC  C2005-077389 [25]
TI   Producing antigenic response, involves contacting antigen-presenting cell
     with A1 adenosine receptor activating agent to increase antigenic
     response of antigen-presenting cell to antigen
DC   B04; D16
IN   BORRON P; WILSON C N; WILSON C
PA   (BORR-I) BORRON P; (ENDA-N) ENDACEA INC; (WILS-I) WILSON C N
CYC  107
PIA  WO 2005026318   A2 20050324 (200525)* EN  56[0]
     US 20050075308  A1 20050407 (200525)  EN
     EP 1651259      A2 20060503 (200629)  EN
ADT  WO 2005026318 A2 WO 2004-US24693 20040730; US 20050075308 A1 Provisional
     US 2003-491510P 20030731; US 20050075308 A1 US 2004-903933 20040730; EP
     1651259 A2 EP 2004-816171 20040730; EP 1651259 A2 WO 2004-US24693 20040730
FDT  EP 1651259      A2 Based on WO 2005026318   A
PRAI US 2003-491510P 20030731
     US 2004-903933 20040730

L3   ANSWER 2 OF 8  WPIDS COPYRIGHT 2007       THE THOMSON CORP on STN
Full Text
AN   2005-152160 [16]   WPIDS
DNC  C2005-049184 [16]
```

TI New xanthine derivatives used for treating e.g. congestive heart failure, hypertension, ischemia-reperfusion organ injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes and cystic fibrosis
DC B02
IN PARTRIDGE J J; **WILSON C N**; PARTRIDGE J; WILSON C
PA (ENDA-N) ENDACEA INC; (PART-I) PARTRIDGE J J; (WILS-I) WILSON C N
CYC 107
PIA WO 2005009343 A2 20050203 (200516)* EN 69[0]
US 20050187226 A1 20050825 (200556) EN
EP 1636229 A2 20060322 (200621) EN
JP 2006527202 W 20061130 (200680) JA 51
ADT WO 2005009343 A2 WO 2004-US18044 20040604; US 20050187226 A1 Provisional US 2003-476684P 20030606; EP 1636229 A2 EP 2004-785932 20040604; US 20050187226 A1 US 2004-861677 20040604; EP 1636229 A2 WO 2004-US18044 20040604; JP 2006527202 W WO 2004-US18044 20040604; JP 2006527202 W JP 2006-515265 20040604
FDT EP 1636229 A2 Based on WO 2005009343 A; JP 2006527202 W Based on WO 2005009343 A
PRAI US 2003-476684P 20030606
US 2004-861677 20040604

L3 ANSWER 3 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2005-057721 [06] WPIDS
DNC C2005-019929 [06]
TI New 3,7-dihydro-purine-2,6-dione derivatives, useful for treating e.g. congestive heart failure, hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury and renal failure, are A1 **adenosine receptor** antagonists
DC B02; K08
IN PARTRIDGE J J; **WILSON C N**; PARTRIDGE J; WILSON C
PA (ENDA-N) ENDACEA INC
CYC 107
PIA WO 2004110379 A2 20041223 (200506)* EN 45[0]
EP 1636230 A2 20060322 (200621) EN
ADT WO 2004110379 A2 WO 2004-US18171 20040607; EP 1636230 A2 EP 2004-754702 20040607; EP 1636230 A2 WO 2004-US18171 20040607
FDT EP 1636230 A2 Based on WO 2004110379 A
PRAI US 2003-476967P 20030609

L3 ANSWER 4 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2004-635530 [61] WPIDS
DNC C2004-228417 [61]
TI New xanthine derivatives are A1 **adenosine receptor** antagonists useful to treat disease e.g. asthma, diabetes, cystic fibrosis, allergic conditions, Adult Respiratory Distress Syndrome (ARDS) and Severe Acute Respiratory Syndrome (SARS)
DC B02
IN PARTRIDGE J J; **WILSON C N**
PA (ENDA-N) ENDACEA INC; (PART-I) PARTRIDGE J J; (WILS-I) WILSON C N
CYC 107
PIA WO 2004074247 A2 20040902 (200461)* EN 41[0]
US 20050119258 A1 20050602 (200537) EN
EP 1601649 A2 20051207 (200580) EN
JP 2006518390 W 20060810 (200654) JA 43
ADT WO 2004074247 A2 WO 2004-US4627 20040217; US 20050119258 A1 Provisional US 2003-448212P 20030219; EP 1601649 A2 EP 2004-711890 20040217; US 20050119258 A1 US 2004-780296 20040217; EP 1601649 A2 WO 2004-US4627 20040217; JP 2006518390 W WO 2004-US4627 20040217; JP 2006518390 W JP 2006-503632 20040217
FDT EP 1601649 A2 Based on WO 2004074247 A; JP 2006518390 W Based on WO 2004074247 A
PRAI US 2003-448212P 20030219
US 2004-780296 20040217

L3 ANSWER 5 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2004-500359 [48] WPIDS
CR 2003-112119
DNC C2004-185379 [48]
TI Treating, preventing or delaying onset of immune system disorder such as AIDS in subject, involves administering A1 **adenosine receptor** antagonist and/or P2X purinoceptor antagonist to subject

DC B07; D16
IN **WILSON C N**
PA (ENDA-N) ENDACEA INC
CYC 1
PIA AU 2003268839 A1 20040122 (200448)* EN 22[0]
ADT AU 2003268839 A1 Div Ex AU 2002-309961 20020517; AU 2003268839 A1 AU 2003-268839 20031215
PRAI AU 2003-268839 20031215
AU 2002-309961 20020517

L3 ANSWER 6 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2004-090679 [09] WPIDS
DNC C2004-036810 [09]
TI Use of **adenosine receptor** antagonist or purinoceptor antagonist for treating purinoceptor-related disorders, e.g. inflammatory disorder
DC B04; D16
IN SIRGO M A; **WILSON C N**
PA (ENDA-N) ENDACEA INC
CYC 101
PIA WO 2003103675 A2 20031218 (200409)* EN 43[0]
AU 2003237460 A1 20031222 (200445) EN
ADT WO 2003103675 A2 WO 2003-US17964 20030606; AU 2003237460 A1 AU 2003-237460 20030606
FDT AU 2003237460 A1 Based on WO 2003103675 A
PRAI US 2002-386769P 20020606

L3 ANSWER 7 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2003-129470 [12] WPIDS
DNC C2003-033214 [12]
DNN N2003-102788 [12]
TI Increasing affinity of A1 **adenosine receptor** ligand for an A1 **adenosine receptor**, useful in the diagnosis and treatment of tumors, involves contacting the ligand with a glycolipid and binding the contacted ligand with the **adenosine receptor**
DC B04; D16; S03
IN **WILSON C N**
PA (ENDA-N) ENDACEA INC; (WILS-I) WILSON C N
CYC 30
PIA WO 2002095391 A1 20021128 (200312)* EN 18[0]
EP 1390740 A1 20040225 (200415) EN
US 20040121406 A1 20040624 (200442) EN
AU 2002311987 A1 20021203 (200452) EN
JP 2005518331 W 20050623 (200546) JA 25
ADT WO 2002095391 A1 WO 2002-US16218 20020523; AU 2002311987 A1 AU 2002-311987 20020523; EP 1390740 A1 EP 2002-739334 20020523; JP 2005518331 W JP 2002-591814 20020523; EP 1390740 A1 WO 2002-US16218 20020523; US 20040121406 A1 WO 2002-US16218 20020523; JP 2005518331 W WO 2002-US16218 20020523; US 20040121406 A1 US 2003-475925 20031024
FDT EP 1390740 A1 Based on WO 2002095391 A; AU 2002311987 A1 Based on WO 2002095391 A; JP 2005518331 W Based on WO 2002095391 A
PRAI US 2001-293362P 20010524
US 2003-475925 20031024

L3 ANSWER 8 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2003-112119 [10] WPIDS
CR 2004-500359
DNC C2003-028754 [10]
TI Treating, preventing or delaying onset of an immune system disorder such as HIV infection, AIDS or ADA SCID using A1 adenosine and P2X purinoceptor antagonists
DC B04; D16
IN **WILSON C N**
PA (ENDA-N) ENDACEA INC; (WILS-I) WILSON C N
CYC 24
PIA WO 2002094317 A1 20021128 (200310)* EN 20[0]
EP 1390068 A1 20040225 (200415) EN
US 20040110774 A1 20040610 (200438) EN
AU 2002309961 A1 20021203 (200452) EN
JP 2004530700 W 20041007 (200466) JA 33
ADT WO 2002094317 A1 WO 2002-US15854 20020517; US 20040110774 A1 Provisional US 2001-292072P 20010518; AU 2002309961 A1 AU 2002-309961 20020517; EP 1390068 A1 EP 2002-736991 20020517; JP 2004530700 W JP 2002-591033

20020517; EP 1390068 A1 WO 2002-US15854 20020517; US 20040110774 A1 CIP of WO 2002-US15854 20020517; JP 2004530700 W WO 2002-US15854 20020517; US 20040110774 A1 US 2003-713860 20031117
FDT EP 1390068 A1 Based on WO 2002094317 A; AU 2002309961 A1 Based on WO 2002094317 A; JP 2004530700 W Based on WO 2002094317 A
PRAI US 2001-292072P 20010518
WO 2002-US15854 20020517
US 2003-713860 20031117

=> d l3,bib,ab,1-8

L3 ANSWER 1 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2005-242392 [25] WPIDS
DNC C2005-077389 [25]
TI Producing antigenic response, involves contacting antigen-presenting cell with A1 **adenosine receptor** activating agent to increase antigenic response of antigen-presenting cell to antigen
DC B04; D16
IN BORRON P; **WILSON C N**; WILSON C
PA (BORR-I) BORRON P; (ENDA-N) ENDACEA INC; (WILS-I) WILSON C N
CYC 107
PIA WO 2005026318 A2 20050324 (200525)* EN 56[0]
US 20050075308 A1 20050407 (200525) EN
EP 1651259 A2 20060503 (200629) EN
ADT WO 2005026318 A2 WO 2004-US24693 20040730; US 20050075308 A1 Provisional US 2003-491510P 20030731; US 20050075308 A1 US 2004-903933 20040730; EP 1651259 A2 EP 2004-816171 20040730; EP 1651259 A2 WO 2004-US24693 20040730
FDT EP 1651259 A2 Based on WO 2005026318 A
PRAI US 2003-491510P 20030731
US 2004-903933 20040730
AB WO 2005026318 A2 UPAB: 20060122
NOVELTY - Producing (M1) an antigenic response, involves contacting an antigen-presenting cell with an A1 **adenosine receptor** activating agent in an amount sufficient to increase the antigenic response of the antigen-presenting cell to the antigen.

DETAILED DESCRIPTION - Producing (M1) an antigenic response, involves:

(a) contacting an antigen-presenting cell with an A1 **adenosine receptor** activating agent in an amount sufficient to increase the antigenic response of the antigen-presenting cell to the antigen;

(b) administering to the subject, an A1 **adenosine receptor** agonist concurrently with an antigen in an amount sufficient to increase the antigenic response of the subject to the antigen, where the antigenic response is produced in a mammalian subject; or

(c) transfecting or electroporating an antigen-presenting cell with a nucleotide sequence encoding an A1 **adenosine receptor** in a manner sufficient to increase the antigenic response of the antigen-presenting cell to antigen.

INDEPENDENT CLAIMS are also included for:

(1) increasing (M2) a cytotoxic response induced by a cytotoxic cell, involves contacting the cytotoxic cell with an A1 **adenosine receptor** activating agent in an amount sufficient to increase the cytotoxic response of the cytotoxic cell;

(2) enhancing (M3) A1 **adenosine receptor** signaling in an antigen-presenting cell, involves administering an activating agent to the antigen-presenting cell in an amount sufficient to enhance A1 **adenosine receptor** signaling in the antigen-presenting cell;

(3) enhancing (M4) signaling between an antigen-presenting cell and an effector cell, involves administering an activating agent in an amount sufficient to enhance signaling between the antigen-presenting cell and the effector cell;

(4) preventing (M5) desensitization of A1 **adenosine receptor** responses, involves administering to an antigen-presenting cell, a desensitizing agent in an amount sufficient to prevent desensitization of A1 **adenosine receptor** responses in the antigen-presenting cell, or transfecting or electroporating the antigen-presenting cell with a nucleotide sequence encoding a protein capable of preventing desensitization of A1 **adenosine receptor** responses;

(5) a composition (C1) comprising an antigen and an activating agent;

(6) a pharmaceutical composition (C2) comprising C1;

(7) determining a subject's responsiveness to treatment for conditions associated with A1 **adenosine receptor** deficiency, involves

determining A1 **adenosine receptor** expression, affinity or function on antigen-presenting cells;

(8) imaging (M6) antigen-presenting cells in vivo in a subject, involves:

(a) obtaining a sample of antigen-presenting cells from a subject, labeling the antigen-presenting cells with a radiolabeled A1 **adenosine receptor** ligand, nucleotide sequence encoding the A1 **adenosine receptor**, and then administering the labeled antigen-presenting cells to the subject in an amount effective to provide a radioimage; or

(b) obtaining a sample of antigen-presenting cells from a subject, and contacting the antigen-presenting cell with a biosensor that recognizes a specific target on the antigen-presenting cell, with the proviso that the biosensor is not a radiolabeled biosensor; and

(9) a diagnostic kit for determining a subject's responsiveness to treatment for conditions associated with A1 **adenosine receptor** deficiency, comprising at least one reagent for determining A1 **adenosine receptor** expression, affinity, or function on antigen-presenting cells of the subject, and printed instructions for assessing the subject's responsiveness to treatment for conditions associated with A1 **adenosine receptor** deficiency, where at least one reagent and the printed instructions are packaged together in a container.

ACTIVITY - CNS-Gen.; Antimicrobial; Immunosuppressive; Muscular-Gen.; Neuroprotective; Antiinflammatory; Vasotropic; Antidiabetic; Cytostatic; Antiasthmatic; Antiallergic; Antiarteriosclerotic.

No supporting data is given.

MECHANISM OF ACTION - Immunestimulator.

USE - (M1) is useful for producing an antigenic response, where the method of producing the antigenic response is performed in combination with known methods of treatment of conditions chosen from immunodeficiency disorders, central nervous system (CNS) disorders, infectious diseases, autoimmune diseases, myasthenia gravis, Crohn's disease, regional enteritis, vasculitis, diabetes mellitus, tumors, cancer, substance abuse, multiple sclerosis, asthma, contact allergy, transplant rejection and atherosclerosis. C1 is useful for immunizing a mammal against an antigen, which involves administering C1. C1 is useful for treating conditions as mentioned above, which involves administering to subject, C1 in an amount sufficient to treat the condition, where the condition is prostate cancer (claimed).

L3 ANSWER 2 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2005-152160 [16] WPIDS
DNC C2005-049184 [16]
TI New xanthine derivatives used for treating e.g. congestive heart failure, hypertension, ischemia-reperfusion organ injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes and cystic fibrosis
DC B02
IN PARTRIDGE J J; **WILSON C N**; PARTRIDGE J; WILSON C
PA (ENDA-N) ENDACEA INC; (PART-I) PARTRIDGE J J; (WILS-I) WILSON C N
CYC 107
PIA WO 2005009343 A2 20050203 (200516)* EN 69[0]
US 20050187226 A1 20050825 (200556) EN
EP 1636229 A2 20060322 (200621) EN
JP 2006527202 W 20061130 (200680) JA 51
ADT WO 2005009343 A2 WO 2004-US18044 20040604; US 20050187226 A1 Provisional US 2003-476684P 20030606; EP 1636229 A2 EP 2004-785932 20040604; US 20050187226 A1 US 2004-861677 20040604; EP 1636229 A2 WO 2004-US18044 20040604; JP 2006527202 W WO 2004-US18044 20040604; JP 2006527202 W JP 2006-515265 20040604
FDT EP 1636229 A2 Based on WO 2005009343 A; JP 2006527202 W Based on WO 2005009343 A
PRAI US 2003-476684P 20030606
US 2004-861677 20040604
AB WO 2005009343 A2 UPAB: 20060121
NOVELTY - Xanthine derivatives (I) are new.

DETAILED DESCRIPTION - Xanthine derivatives of formula (I) and their salts, solvates, hydrates and prodrugs are new. (I) Optionally have at least one radioactive or non-radioactive label group. The label groups are optionally connected to (I) through at least one spacer group.

R1 = 1-8C alkyl (optionally substituted by at least one OR5, NR6R7 or halo);

R5, R6 = H or 1-8C alkyl;

R7 = H, 1-8C alkyl or Alk1-OH;

Alk1 = 1-8C alkylene;
R2 = T1, Alk11N(CH3)Alk12OH or Alk13NR14R15;
T1 = H, 1-8C alkyl, Alk2COOH, Alk3COOR8, Alk4CONR9R10, Alk5OH, Alk6SO3H, Alk7PO3H2, Alk8OR11, Alk9OH or Alk10NR12R13;
Alk2-Alk13 = 1-8C alkylene or alkenylene;
m, q, t = 1-8;
Q = H, OH, NH2, (CH2)tOH, or R13aCOOH;
R8-R13, R13a = H or 1-8C alkyl;
R14 = H, CH3 or (CH2)p1CH3;
R15 = H, CH3, (CH2)p2CH3 or (CH2)mOH;
p1, p2 = 1-7;
R3 = Alk14ArR16;
Alk14 = 1-8C alkylene or alkenylene;
Ar = 5- or 6-membered aromatic ring optionally containing 1-4 N, O or S heteroatoms or bicyclic 9 or 11 membered aromatic ring optionally containing 1-6 N, O or S heteroatoms;
R16 = H, OH, OR13b, NO2, NH2, CN, Alk15OH, Alk16NH2, NR17R18, NR19COR19a, Alk17COOR19b, SO2R19c, SO3H, PO3H2 or halo;
Alk15-Alk17 = 1-8C alkylene or alkenylene;
R13b = H or 1-8C alkyl;
R17-R19, R19a-R19c = H, aromatic group or 1-8C alkyl;
R4 = (CH2)r-phenyl (substituted by R20);
r = 1-20;
R20 = T2, H, OH, NH2, Alk19OH, Alk20NH2 or Alk21COOH;
T2 = SO3H, PO3H2, halo, OR13c, COOR13d, NO2, NR21R22, NR23COR23a, Alk18COOR19d, SO2R19e or Alk18NR24R25;
Alk19-Alk21 = 1-8C alkylene or alkenylene;
R13c, R13d = 1-8C alkyl;
R19d, R19e = H, aromatic group or 1-8C alkyl, and
R21-R25, R23a = H, aromatic group or 1-8C alkyl,
pProvided that:
(1) when R3 is (CH2)q(C6H4)Q, then R2 is T1 or Alk11N(CH3)Alk12OH;
(2) when R3 is not (CH2)q(C6H4)Q, then R2 is T1 or Alk13NR14R15, and
(3) when R3 is not (CH2)q(C6H4)Q, then R20 is T2, H, OH, NH2, Alk19OH, Alk20NH2 or Alk21COOH.

INDEPENDENT CLAIMS are also included for:
(1) a diagnostic assay-type probe of (I);
(2) an imaging agent for **adenosine receptors** comprising (I), where at least one of its atoms or at least one atom bonded with it is radioactively and/or spin labeled, and
(3) treatment of A1 **adenosine receptor** related disorders which comprises administering (I) optionally in combination with at least one therapeutic agent.

ACTIVITY - Cardiovascular-Gen.; Hypotensive; Vasotropic; Nephrotropic; Neuroprotective; Nootropic; Antidepressant; Anorectic; Antiasthmatic; Antidiabetic; CNS-Gen.; Respiratory-Gen.; Cardiant; Vasotropic; Antiallergic; Immunosuppressive; Antiinflammatory; Antitussive; Gastrointestinal-Gen.; Anti-HIV; Antibacterial; Antiaddictive; Antiparkinsonian.

No biological data is given.

MECHANISM OF ACTION - A1 **adenosine receptor** antagonist.

USE - Used for treating congestive heart failure, hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, autoimmune disorders, inflammatory disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, post-operative ileus, fibrosis, sclerosis, Adult Respiratory Distress Syndrome (ARDS), acquired immunodeficiency syndrome (AIDS), Acute Lung Injury (ALI), acquired immunodeficiency syndrome (AIDS), Severe Acute Respiratory Syndrome (SARS), septicemia, substance abuse, drug dependence and Parkinson's disease and are also useful as diagnostic agents (claimed).

ADVANTAGE - (I) Exhibit good water solubility.

L3 ANSWER 3 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2005-057721 [06] WPIDS
DNC C2005-019929 [06]
TI New 3,7-dihydro-purine-2,6-dione derivatives, useful for treating e.g. congestive heart failure, hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury and renal failure, are A1 **adenosine receptor** antagonists
DC B02; K08
IN PARTRIDGE J J; **WILSON C N**; PARTRIDGE J; WILSON C

PA (ENDA-N) ENDACEA INC
CYC 107
PIA WO 2004110379 A2 20041223 (200506)* EN 45[0]
EP 1636230 A2 20060322 (200621) EN
ADT WO 2004110379 A2 WO 2004-US18171 20040607; EP 1636230 A2 EP 2004-754702 20040607; EP 1636230 A2 WO 2004-US18171 20040607
FDT EP 1636230 A2 Based on WO 2004110379 A
PRAI US 2003-476967P 20030609
AB WO 2004110379 A2 UPAB: 20060121
NOVELTY - 3,7-Dihydro-purine-2,6-dione derivatives (I) are new.
DETAILED DESCRIPTION - 3,7-Dihydro-purine-2,6-dione derivatives of formula (I) and their salts, solvates and hydrates are new.
R1 = 1-8C alkyl;
R2 = (CH2)nN(R5)R6;
R5 = H or (CH2)pCH3;
R6 = H or (CH2)mOH;
p = 1-7;
R3 = (CH2)q-C6H4-R7;
R7 = H, OH, NH2, (CH2)tOH or R9COOH;
R9 = straight or branched 1-8C alkylene or 1-8C alkenylene;
R4 = -(CH2)r-phenylene (substituted at ortho or meta position by R8);
R8 = H, OH, (CH2)fNH2, (CH2)sOH or R10COOH;
f = 0 - 8;
n, m, q, t, r, s = 1-8;and
R10 = 1-8C alkylene or alkenylene.
INDEPENDENT CLAIMS are also included for:
(1) diagnostic assay-type probe of (I) where the compound is labeled by a radioactive or non-radioactive material (preferably radioactive material) or optionally connected to (I) by a spacer component present on it where the spacer component has functionality which bonds to the amine, hydroxyl, or carboxyl functionality present on the R7 or R8 substituent of (I);
(2) an imaging agent for **adenosine receptors** comprising (I), where at least one of its atoms or at least one atom bonded to it has radioactively and/or spin labeled; and
(3) preparation of (I).
ACTIVITY - Cardiant; Hypotensive; Vasotropic; Nootropic; Neuroprotective; Antidepressant; Anorectic; Antiasthmatic; Antidiabetic; CNS-Gen.; Respiratory-Gen.; Antiallergic; Immunosuppressive; Nephrotropic; Antiinflammatory; Antitussive; Anti-HIV; Antibacterial; Antiaddictive; Antiparkinsonian.
MECHANISM OF ACTION - A1 **adenosine receptor** antagonist; CNS stimulants.
USE - As diagnostic assay-type probes; as an imaging agent for **adenosine receptors**; for treating A1 **adenosine receptor** related disorders e.g. congestive heart failure, hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions (including allergic rhinitis and anaphylactic shock), autoimmune disorders, inflammatory disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, Adult Respiratory Distress Syndrome (ARDS), acquired immunodeficiency syndrome (AIDS), Acute Lung Injury (ALI), Severe Acute Respiratory Syndrome (SARS), septicemia, substance abuse, drug dependence or Parkinson's disease in a mammal e.g. human (claimed) and as imaging agent useful in diagnostic procedures such as magnetic resonance imaging (MRI) and positron emission tomography (PET) and in cell or receptor based assay.
ADVANTAGE - (I) are potent and selective antagonists of A1 **adenosine receptors**.

L3 ANSWER 4 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2004-635530 [61] WPIDS
DNC C2004-228417 [61]
TI New xanthine derivatives are A1 **adenosine receptor** antagonists useful to treat disease e.g. asthma, diabetes, cystic fibrosis, allergic conditions, Adult Respiratory Distress Syndrome (ARDS) and Severe Acute Respiratory Syndrome (SARS)
DC B02
IN PARTRIDGE J J; **WILSON C N**
PA (ENDA-N) ENDACEA INC; (PART-I) PARTRIDGE J J; (WILS-I) WILSON C N
CYC 107
PIA WO 2004074247 A2 20040902 (200461)* EN 41[0]

US 20050119258 A1 20050602 (200537) EN
EP 1601649 A2 20051207 (200580) EN
JP 2006518390 W 20060810 (200654) JA 43

ADT WO 2004074247 A2 WO 2004-US4627 20040217; US 20050119258 A1 Provisional US 2003-448212P 20030219; EP 1601649 A2 EP 2004-711890 20040217; US 20050119258 A1 US 2004-780296 20040217; EP 1601649 A2 WO 2004-US4627 20040217; JP 2006518390 W WO 2004-US4627 20040217; JP 2006518390 W JP 2006-503632 20040217

FDT EP 1601649 A2 Based on WO 2004074247 A; JP 2006518390 W Based on WO 2004074247 A

PRAI US 2003-448212P 20030219
US 2004-780296 20040217

AB WO 2004074247 A2 UPAB: 20060203

NOVELTY - Xanthine derivatives (I) and their salts, hydrates and prodrugs are new.

DETAILED DESCRIPTION - Xanthine derivatives of formula (I) and their acceptable salts, hydrates and prodrugs are new.

A, A' = 5-6 membered (hetero)aromatic ring containing 0-4 heteroatoms of N, O or S; either

R1 or R2 = (CH2)r-A'-R4; or

R1 = 1-8C alkanyl, 2-8C alkenyl, 2-8C alkynyl (all optionally substituted with CN, CH2NR6R7OH, OR8, NR6R7, NHCOR8, NHCONR6R7, halo, OCOR8, OCH2COOH, OCH2COOR8, SO2R5, S-R5, NHCONH phenyl, OCH2-CONR6R7, OCH2CH2OH, SO2-CH2-CH2-O-COR8, OCH2-CH2-NR6R7, SO2-CH2-CH2-OH, CONHSO2R8, CH2CONHSO2R8, OCH2CH2OR8, COOH, COOR8, CONR6R7, CHO, SR8, SOR8, SO2R8, SO3H, PO3H2, SO2NR6R7, OCH2-CH2OCOR8, CH=NOH, CH=NOR8, COR9, CH(OH)R9, CH(OR8)2, CH=CH-R10, OCONR6R7, HC-N-NH-R11, NH-CH-NH2, NH-CH-NH-NH2, by 1,3-dioxolane or 1,3-dioxane (which is optionally mono- or poly substituted by methyl)), phenyl-1-6C alkylene, phenyl-2-6C alkenylene or phenyl-2-6C alkynylene (the phenyl ring is optionally substituted, either directly or via a 1-4C alkylene, with one or more of the following groups: 1-3C alkyl, CN, CH2NR6R7, NO2, OH, OR8, CH2-NH-SO2-R8, NHCOR8, NHCONR6R7, halo, OCOR8, OCH2COOH, OCH2COOR8, CH2OCOR8, SO2R5, OCH2-CONR6R7, OCH2CH2OH, OCH2-CH2-NR6R7, CONHSO2R8, OCH2CH2OR8, COOH, COOR8, CF3, cyclopropyl, CONR6R7, CH2OH, CH2OR8, CHO, SR8, SOR8, SO2R8, SO3H, PO3H2, SO2NR6R7, OCH2-CH2OCOR8, CH=NOH, CH=NOR8, COR9, CH(OH)R9, CH(OR8)2, NHCOOR8, CH2CONHSO2R8, CH=CH-R10, OCONR6R7, CH2-O-CONR6R7, CH2-CH2-O-CONR6R7, HC-N-NH-R11, NH-CH-NH2, NH-CH-NH-NH2, by 1,3-dioxolane or 1,3-dioxane (which is optionally mono- or polysubstituted by methyl)), 3-7C cycloalkyl-1-6C alkylene, 3-7C cycloalkyl-2-6C alkenylene, 3-7C cycloalkyl-2-6C alkynylene (the cycloalkyl group optionally substituted, either directly or via a 1-4C alkylene group, by CN, CH2NR6R7, O, OH, OR8, NR6R7, NHCOR8, NHCONR6R7, halo, OCOR8, OCH2COOH, OCH2COOR8, CH2OCOR8, SO2R5, OCH2CONR6R7, OCH2CH2OH, OCH2-CH2-NR6R7, OCH2CH2OR8, COOH, COOR8, CONR6R7, CH2OH, CH2OR8, CHO, SR8, SOR8, SO2R8, SO3H, PO3H2, SO2NR6R7, OCH2-CH2-OCOR8, CH=NOH, CH=NOR8, COR9, CH(OH)R9, CONHSO2R8, CH(OR8)2, NHCOOR8, CH=CH-R10, OCONR6R7, CH2-O-CONR6R7, CH2-CH2-O-CONR6R7, HC-N-NH-R11, NH-CH-NH2, NH-CH-NH-NH2, by 1,3-dioxolane or 1,3-dioxane (which is optionally mono- or polysubstituted by methyl)) or formula A-1-6C alkylene, A-CONH-1-6C alkylene, ACONH-2-6C alkenylene, A-CONH-2-6C alkynylene, A-NH-CO-1-6C alkylene, ANH-CO-2-6C alkenylene, A-NH-CO-2-6C alkynylene, A-2-6C alkenylene or A-2-6C alkynylene;

r = 1-20;

R4 = H, NH2, (CH2)sOH, R14COOH, halo, NHR8, NR8R9, NHCOR8, NR8COR9, SO3H or PO3H2;

s = 1-8;

R14 = 1-8C alkyl or 1-8C alkylidene;

R3 = H, NH2, R15COOH, halo, NHR8, NR8R9, NHCOR8, NR8COR9, SO3H or PO3H2;

R15 = 1-8C alkyl or 1-8C alkylidene or (CH2) tOH;

t = 1-8;

q = 1-8;

A = C or N-linked 5-6 membered heterocyclic ring, 5-6 membered aromatic ring or 5-6 membered heteroaromatic ring which contains N, O or S as heteroatoms or optionally mono- or poly substituted with 1-4C alkyl, halo, OR8, CN, NO2, NH2, CH2NR6R7, OH, O, a ketal, COOH, SO3H, PO3H2, COOR8, CONR6R7, COR9, SO2-R8, CONR6R7 or dioxane derivative of formula (a);

R5 = 1-4C alkyl (optionally substituted with OH, OCOR8, NH2, NR6R7 or NHCOR8); either

R6 = 3-6C cycloalkyl (optionally substituted), H, alkyl, alkenyl or alkynyl group having up to 10C atoms (preferably 1-4C alkyl group, which optionally substituted with OH, phenyl (optionally substituted), NH2 (optionally substituted), 1-8C or it denotes (CH2)m-NHCOOR8; and

R7 = 3-6C cycloalkyl (optionally substituted), H, alkyl, alkenyl or

alkynyl group having up to 10C atoms (which optionally substituted with OH, phenyl (optionally substituted) amino (optionally substituted), 1-8C or it denotes (CH2)m-NHCOOR8; or

NR6R7 = optionally saturated 5-6 membered ring which may contain as heteroatoms N, O or S, while the heterocyclic ring substituted with 1-4C alkyl or may carry one of the following groups (CH2)n-NH2, O, a ketal - preferably -O-CH2-CH2-O-, (CH2)n-NH-1-4C alkyl, (CH2)n-N(1-8C alkyl), (CH2)n-NHCOOR8, halo, OR8, CN, NO2, NH2, CH2NR6R7, OH, COOH, SO3H, PO3H2, COOR8, CONR6R7 or SO2R8;

m = 1-4;

n = 2-4;

R8 = 2-8C alkenyl (optionally substituted with CO2H, benzyl or phenyl (which is optionally mono- or polysubstituted by OCH3)), H or 1-8C alkyl;

R9 = phenyl, benzyl (both optionally substituted), 2-8C alkynyl (optionally substituted with CO2H), 1-8C alkyl, 2-8C alkenyl or 3-6C cycloalkyl; and

R10 = phenyl (optionally substituted), COOR8, CH2OR8, CONR6R7, H, 1-3C alkyl or CH2NR6R7.

ACTIVITY - Antiallergic; Antiinflammatory; CNS-Gen.; Uropathic; Antiasthmatic; Cardiovascular-Gen.; Hypotensive; Antidiabetic; Respiratory-Gen.; Antibacterial; Immunosuppressive; Antiaddictive; Antiparkinsonian. No biological data given.

MECHANISM OF ACTION - A1 **adenosine receptor** antagonists.

USE - (I) are useful as anti-allergenics, anti-inflammatory agents, CNS stimulants, diuretics, antiasthmatics, cardiotonics. (I) are also useful to treat A1 **adenosine receptor** related disorders e.g. hypertension, asthma, diabetes, cystic fibrosis, allergic conditions, Adult Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), Severe Acute Respiratory Syndrome (SARS), septicemia, substance abuse, drug dependence, and Parkinson's disease.

ADVANTAGE - (I) has a good water solubility.

L3 ANSWER 5 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2004-500359 [48] WPIDS
CR 2003-112119
DNC C2004-185379 [48]
TI Treating, preventing or delaying onset of immune system disorder such as AIDS in subject, involves administering A1 **adenosine receptor** antagonist and/or P2X purinoceptor antagonist to subject
DC B07; D16
IN **WILSON C N**
PA (ENDA-N) ENDACEA INC
CYC 1
PIA AU 2003268839 A1 20040122 (200448)* EN 22[0]
ADT AU 2003268839 A1 Div Ex AU 2002-309961 20020517; AU 2003268839 A1 AU 2003-268839 20031215
PRAI AU 2003-268839 20031215
AU 2002-309961 20020517
AB AU 2003268839 A1 UPAB: 20050530

NOVELTY - Treating, preventing or delaying (M1) onset of immune system disorder in subject, comprising administering a compound chosen from A1 **adenosine receptor** antagonists, P2X purinoceptor antagonists, and combination of one or more of A1 **adenosine receptor** antagonists and P2X purinoceptor antagonists, to treat, prevent or delay the onset of immune system disorder, is new.

ACTIVITY - Anti-HIV; Immunostimulant.

MECHANISM OF ACTION - A1 **adenosine receptor** and P2X purinoceptor antagonists (claimed); Inhibits HIV-induced upregulation of chemokine receptors in monocytes, macrophages and T cells.

No biological data is given.

USE - (M1) is useful for treating, preventing or delaying onset of immune system disorder, preferably treating HIV infection or AIDS, or adenosine deaminase deficiency-dependent-severe immunodeficiency disease (ADA-SCID), in a subject, where the treatment is carried out in conjunction with another treatment for HIV infection or AIDS, or ADA-SCID. The A1 **adenosine receptor** antagonist is an antibody that binds to A1 **adenosine receptor**. The P2X purinoceptor antagonist is an antibody that binds to P2X purinoceptor. (All claimed.)

L3 ANSWER 6 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2004-090679 [09] WPIDS
DNC C2004-036810 [09]

TI Use of **adenosine receptor** antagonist or purinoceptor antagonist for treating purinoceptor-related disorders, e.g. inflammatory disorder
DC B04; D16
IN SIRGO M A; **WILSON C N**
PA (ENDA-N) ENDACEA INC
CYC 101
PIA WO 2003103675 A2 20031218 (200409)* EN 43[0]
AU 2003237460 A1 20031222 (200445) EN
ADT WO 2003103675 A2 WO 2003-US17964 20030606; AU 2003237460 A1 AU 2003-237460 20030606
FDT AU 2003237460 A1 Based on WO 2003103675 A
PRAI US 2002-386769P 20020606
AB WO 2003103675 A2 UPAB: 20050906
NOVELTY - Treatment of purinoceptor-related disorders involves administration of an A1 **adenosine receptor** antagonist or a P2x purinoceptor antagonist with at least one additional agent.
ACTIVITY - Antiinflammatory; Cardiant; Hypotensive; Vasotropic; Antibacterial; Immunosuppressive; Antiallergic; Nootropic; Neuroprotective; Antidepressant; Anorectic; Antiasthmatic; Antidiabetic; Respiratory-Gen.; Antitussive; Neuroprotective; Antiaddictive; Antiparkinsonian.
MECHANISM OF ACTION - A1 Antagonist; P2x Purinoceptor Antagonist.
Compounds (I) antagonized human L-97-1 **adenosine receptor** with an IC50 value of 2.077 microM. against ligand.
USE - For treating purinoceptor-related disorders, e.g. inflammatory disorder, congestive heart failure, systemic hypertension, pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin related tissue injury, anaphylactic shock, allergic rhinitis, Alzheimer's disease, depression, obesity, asthma (e.g. intrinsic asthma and extrinsic asthma), diabetes, cystic fibrosis, allergic conditions, autoimmune disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, fibrosis, sclerosis, renal failure, adult respiratory distress syndrome (ARDS), Severe Acute Respiratory Syndrome (SARS), Acute Lung Injury (ALI), septicemia, substance abuse, drug dependence, and Parkinson's disease (all claimed).
ADVANTAGE - The method does not exhibit any side effects.

L3 ANSWER 7 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2003-129470 [12] WPIDS
DNC C2003-033214 [12]
DNN N2003-102788 [12]
TI Increasing affinity of A1 **adenosine receptor** ligand for an A1 **adenosine receptor**, useful in the diagnosis and treatment of tumors, involves contacting the ligand with a glycolipid and binding the contacted ligand with the **adenosine receptor**
DC B04; D16; S03
IN **WILSON C N**
PA (ENDA-N) ENDACEA INC; (WILS-I) WILSON C N
CYC 30
PIA WO 2002095391 A1 20021128 (200312)* EN 18[0]
EP 1390740 A1 20040225 (200415) EN
US 20040121406 A1 20040624 (200442) EN
AU 2002311987 A1 20021203 (200452) EN
JP 2005518331 W 20050623 (200546) JA 25
ADT WO 2002095391 A1 WO 2002-US16218 20020523; AU 2002311987 A1 AU 2002-311987 20020523; EP 1390740 A1 EP 2002-739334 20020523; JP 2005518331 W JP 2002-591814 20020523; EP 1390740 A1 WO 2002-US16218 20020523; US 20040121406 A1 WO 2002-US16218 20020523; JP 2005518331 W WO 2002-US16218 20020523; US 20040121406 A1 US 2003-475925 20031024
FDT EP 1390740 A1 Based on WO 2002095391 A; AU 2002311987 A1 Based on WO 2002095391 A; JP 2005518331 W Based on WO 2002095391 A
PRAI US 2001-293362P 20010524
US 2003-475925 20031024
AB WO 2002095391 A1 UPAB: 20060118
NOVELTY - Increasing (M1) affinity of an A1 **adenosine receptor** (A1AR) ligand for an A1 **adenosine receptor** comprises:
(a) contacting the A1AR ligand with a glycolipid or its analog, and binding the contacted A1AR ligand with A1AR;
(b) contacting the A1AR with a glycolipid or its analog, and binding the contacted A1AR with A1AR ligand; or
(c) concurrently contacting the A1AR, A1AR ligand and the glycolipid or its analog.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a pharmaceutical formulation (preferably liposomal formulation) comprising the A1AR ligand, the glycolipid or its analog in an amount to enhance binding of the A1AR ligand for the A1AR and a carrier; and

(2) a method for increasing the affinity of an A1AR ligand for a binding site polypeptide of A1AR comprises:

(a) contacting the binding site polypeptide of an A1AR ligand with a glycolipid or its analog; and

(b) binding the contacted binding site polypeptide of an A1AR with an A1AR ligand.

ACTIVITY - Antiasthmatic; Antiarrhythmic; Analgesic; Anticonvulsant; Cardiant; Neuroprotective; Antilipemic; Antidiabetic; Gastrointestinal-Gen.; Antidiarrheic; Antiinflammatory; Vasotropic; Hepatotropic; Nephrotropic; Antibacterial; Immunosuppressive; Anti-HIV; Cytostatic.

No supporting data provided.

MECHANISM OF ACTION - A1 **adenosine receptor** (A1AR) ligand binding enhancer.

NBD-Galactocerebroside (100 mug/ml) increases (125I) BWA84U binding in human PAECs by approximately 75%.

USE - For increasing the affinity of an A1 **adenosine receptor** (A1AR) ligand for A1AR, for delivering the A1AR ligand for carrying out a diagnostic test, and for administering the A1AR ligand to a subject to be treated (claimed), in both medical and veterinary uses. The method is useful in diagnostic methods in diagnosis of tumor involving in vitro radiolabeling the macrophages, monocytes and splenocytes of a patient, for testing the cytotoxicity of diagnostic cells (e.g. monocytes, macrophages, promonocytes, peripheral blood stem cells, hematopoietic stem cells), or for measuring the ability of the diagnostic cells to bind MCP-1 protein or annexins.

A1AR ligands can also be used as diuretics, bronchodilators, as antiasthmatics; in the treatment of adenosine-sensitive cardiac arrhythmias; for antinociception (e.g. analgesics), anticonvulsants; for cardioprotection both short term (e.g. prior to percutaneous angioplasty (PTCA), angioplasty, and cardiac surgeries) and long term (prevention of myocardial infarction and reduction of infarct damage, especially in high risk patients); for neuroprotection (e.g. stroke prevention, and treatment, epilepsy); for pain management including different forms of neuropathic pain (e.g: diabetic neuropathy), post herpetic neuralgia; in antilipid uses such as reduction of free fatty acids, triglycerides, glucose; for adjunct therapy in diabetes, including insulin and non-insulin dependent diabetes mellitus; for treatment of GI disorders (e.g. diarrhea, irritable bowel disease, irritable bowel syndrome, and incontinence), glaucoma, sleep apnea, cardiac disarrythmias (e.g. paroxysmal supraventricular tachycardia); for use in combination with anesthesia for post surgical pain; for treatment of inflammation, kidney and liver disorders; for treatment of sepsis, septicemia, endotoxemia, endotoxin-induced organ/tissue injury, and ischemia-reperfusion organ/tissue injury; for treatment and prevention of fibrosis and sclerosis; for treatment of AIDS and other immune disorders; and for treatment of tumors and cancers.

ADVANTAGE - The method increases the affinity of the A1AR ligand for a binding site polypeptide of the A1AR, compared to the prior art methods of delivering A1AR ligands, which results in the increase in the efficiency of the delivery of the drug to the cell, tissue or subject, increased uptake of the ligands across the blood-brain barrier and tissue barriers e.g. liver, gut, skin, vagina, mucosal of the respiratory tract (such as mucosal of nose, mouth, trachea and bronchi) and brain, and increases the bioavailability and solubility of the ligand to the target cell receptor protein, membrane, tissue or subject. The increase in bioavailability and solubility results in the decrease in the amount of the ligand. The combination or conjugation of the glycolipid with the ligands also allows for an alteration in the solubility of the ligand (e.g. an alteration from a water-soluble ligand to a non-water soluble ligand).

L3 ANSWER 8 OF 8 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 2003-112119 [10] WPIDS
CR 2004-500359
DNC C2003-028754 [10]
TI Treating, preventing or delaying onset of an immune system disorder such as HIV infection, AIDS or ADA SCID using A1 adenosine and P2X purinoceptor antagonists
DC B04; D16
IN **WILSON C N**

PA (ENDA-N) ENDACEA INC; (WILS-I) WILSON C N
CYC 24
PIA WO 2002094317 A1 20021128 (200310)* EN 20[0]
EP 1390068 A1 20040225 (200415) EN
US 20040110774 A1 20040610 (200438) EN
AU 2002309961 A1 20021203 (200452) EN
JP 2004530700 W 20041007 (200466) JA 33
ADT WO 2002094317 A1 WO 2002-US15854 20020517; US 20040110774 A1 Provisional US 2001-292072P 20010518; AU 2002309961 A1 AU 2002-309961 20020517; EP 1390068 A1 EP 2002-736991 20020517; JP 2004530700 W JP 2002-591033 20020517; EP 1390068 A1 WO 2002-US15854 20020517; US 20040110774 A1 CIP of WO 2002-US15854 20020517; JP 2004530700 W WO 2002-US15854 20020517; US 20040110774 A1 US 2003-713860 20031117
FDT EP 1390068 A1 Based on WO 2002094317 A; AU 2002309961 A1 Based on WO 2002094317 A; JP 2004530700 W Based on WO 2002094317 A
PRAI US 2001-292072P 20010518
WO 2002-US15854 20020517
US 2003-713860 20031117
AB WO 2002094317 A1 UPAB: 20051109
NOVELTY - Treating, preventing or delaying onset of an immune system disorder such as HIV infection, AIDS or an adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject, is new.
DETAILED DESCRIPTION - Treating, preventing or delaying onset of an immune system disorder such as HIV infection, AIDS or an adenosine deaminase deficiency-dependent severe immunodeficiency disease (ADA SCID) in a subject, comprises administering a compound that is an A1 **adenosine receptor** antagonists, P2X purinoceptor antagonists, or a combination of at least one of both, where the compound is administered to treat, prevent or delay the onset of an immune system disorder such as HIV infection, AIDS or ADA SCID.
ACTIVITY - Immunosuppressive; Anti-HIV; Cytostatic; Virucide. No biological data given.
MECHANISM OF ACTION - Adenosine-Antagonist-A1; P2-Antagonist.
USE - The methods and compositions of the present invention are useful for treating, preventing or delaying onset of an immune system disorder such as HIV infection, AIDS or ADA SCID (claimed). Other immunodeficiency disorder include herpes virus infections, Epstein-Barr virus infections, lepromatous leprosy, various forms of congenital or genetically determined hematopoietic abnormalities like severe leukemias and aplastic anemia, Wiskott-Aldrich syndrome, Blackfan-Diamond syndrome, Fanconi anemia, severe neutrophils dysfunction, severe agranulocytosis, infantile and late onset osteopetrosis and Burkitt's lymphoma.

=> file medline
COST IN U.S. DOLLARS SINCE FILE ENTRY 81.52 TOTAL SESSION 92.20
FULL ESTIMATED COST

FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007

FILE LAST UPDATED: 6 Jan 2007 (20070106/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> e wilson c n/au
E1 1 WILSON C M Y/AU
E2 1 WILSON C MORGAN/AU
E3 96 --> WILSON C N/AU
E4 11 WILSON C O/AU
E5 31 WILSON C P/AU
E6 96 WILSON C R/AU
E7 2 WILSON C RON/AU
E8 1 WILSON C RONALD/AU
E9 75 WILSON C S/AU
E10 10 WILSON C T/AU
E11 1 WILSON C V/AU

```
E12         199      WILSON C W/AU

=> s e3
L4           96 "WILSON C N"/AU

=> s l4 and (adenosine receptor? or P2? receptor? or P2? purinoceptor?)
        155447 ADENOSINE
        779544 RECEPTOR?
          5520 ADENOSINE RECEPTOR?
                 (ADENOSINE(W)RECEPTOR?)
         61228 P2?
        779544 RECEPTOR?
          3123 P2? RECEPTOR?
                 (P2?(W)RECEPTOR?)
         61228 P2?
          3726 PURINOCEPTOR?
          1331 P2? PURINOCEPTOR?
                 (P2?(W)PURINOCEPTOR?)
L5              1 L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEPTOR
                  ?)

=> d l5,cbib,ab

L5   ANSWER 1 OF 1      MEDLINE on STN
2005500651.     PubMed ID: 16020631.   A novel A1 adenosine receptor
     antagonist, L-97-1 [3-[2-(4-aminophenyl)-ethyl]-8-benzyl-7-{2-ethyl-(2-
     hydroxy-ethyl)-amino]-ethyl}-1-propyl-3,7-dihydro-purine-2,6-dione],
     reduces allergic responses to house dust mite in an allergic rabbit model
     of asthma. Obiefuna P C M; Batra V K; Nadeem A; Borron P; Wilson C N;
     Mustafa S Jamal. (Department of Pharmacology, East Carolina University,
     Greenville, North Carolina, USA. ) The Journal of pharmacology and
     experimental therapeutics, (2005 Oct) Vol. 315, No. 1, pp. 329-36.
     Electronic Publication: 2005-07-14. Journal code: 0376362. ISSN:
     0022-3565. Pub. country: United States. Language: English.
AB   Adenosine, an important signaling molecule in asthma, produces
     bronchoconstriction in asthmatics. Adenosine produces bronchoconstriction
     in allergic rabbits, primates, and humans by activating A1 adenosine
     receptors (ARs). Effects of L-97-1 [3-[2-(4-aminophenyl)-ethyl]-8-
     benzyl-7-{2-ethyl-(2-hydroxyethyl)-amino]-ethyl}-1-propyl-3,7-dihydro-
     purine-2,6-dione] a water-soluble, small molecule A1 AR antagonist were
     investigated on early and late phase allergic responses (EAR and LAR) in a
     hyper-responsive rabbit model of asthma. Rabbits were made allergic by
     intraperitoneal injections of house dust mite [HDM; 312 allergen units
     (AU)] extract within 24 h of their birth. Booster HDM injections were
     given weekly for 1 month, biweekly for 4 months, and continued monthly
     thereafter. Hyperresponsiveness was monitored by measuring lung dynamic
     compliance (Cdyn), after histamine or adenosine aerosol challenge in
     allergic rabbits. Hyper-responsive rabbits were subjected to aerosol of
     HDM (2500 AU), 1 h after intragastric administration of L-97-1 (10 mg/kg)
     solution or an equivalent volume of saline. Cdyn was significantly higher
     after treatment with L-97-1 compared with untreated controls (p < 0.05 n =
     5). Histamine PC30 was significantly higher (p < 0.05; n = 5) after
     L-97-1 at 24 h compared with histamine PC30 at 24 h after HDM. Adenosine
     PC30 was significantly higher at 15 min and 6 h after L-97-1 compared with
     control (p < 0.05; n = 5). L-97-1 showed strong affinity for human A1 ARs
     in radioligand binding studies and no inhibition toward human
     phosphodiesterase II, III, IV, and V enzymes. These data suggest that
     L-97-1 produces a significant reduction of histamine or adenosine-induced
     hyper-responsiveness and HDM-induced EAR and LAR in allergic rabbits by
     blocking A1 ARs and may be beneficial as an oral therapy for human asthma.


=> d his

     (FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

     FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
               E WILSON CONSTANCE N/IN
L1              3 S E4

     FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
               E WILSON C N/IN
L2             19 S E3
L3              8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP
```

```
     FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
                E WILSON C N/AU
L4            96 S E3
L5             1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.00      93.20

FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 4 Jan 2007 (20070104/PD)
FILE LAST UPDATED: 4 Jan 2007 (20070104/ED)
HIGHEST GRANTED PATENT NUMBER: US7159245
HIGHEST APPLICATION PUBLICATION NUMBER: US2007006355
CA INDEXING IS CURRENT THROUGH 4 Jan 2007 (20070104/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 4 Jan 2007 (20070104/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006


=> s (adenosine receptor? or P2? purinoceptor? or P2X receptor?)
         30428 ADENOSINE
        158278 RECEPTOR?
          1813 ADENOSINE RECEPTOR?
                 (ADENOSINE(W)RECEPTOR?)
        131597 P2?
           371 PURINOCEPTOR?
           190 P2? PURINOCEPTOR?
                 (P2?(W)PURINOCEPTOR?)
           722 P2X
        158278 RECEPTOR?
           248 P2X RECEPTOR?
                 (P2X(W)RECEPTOR?)
L6         2132 (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)

=> s l6 and antagonist?
         81380 ANTAGONIST?
L7        1803 L6 AND ANTAGONIST?

=> s l7 and (adenosine receptor?/clm or P2? purinoceptor?/clm or P2X receptor?/clm)
          2936 ADENOSINE/CLM
         33486 RECEPTOR?/CLM
           322 ADENOSINE RECEPTOR?/CLM
                 ((ADENOSINE(W)RECEPTOR?)/CLM)
          5939 P2?/CLM
            39 PURINOCEPTOR?/CLM
             5 P2? PURINOCEPTOR?/CLM
                 ((P2?(W)PURINOCEPTOR?)/CLM)
            56 P2X/CLM
         33486 RECEPTOR?/CLM
            15 P2X RECEPTOR?/CLM
                 ((P2X(W)RECEPTOR?)/CLM)
L8          319 L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P2X
                RECEPTOR?/CLM)

=> s l8 and antagonist?/clm
         13091 ANTAGONIST?/CLM
L9         140 L8 AND ANTAGONIST?/CLM

=> s l9 and ay<2002
       3511059 AY<2002
L10         61 L9 AND AY<2002

=> d his

     (FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

     FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
                E WILSON CONSTANCE N/IN
L1            3 S E4

     FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
```

```
              E WILSON C N/IN
L2           19 S E3
L3            8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
              E WILSON C N/AU
L4           96 S E3
L5            1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6         2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7         1803 S L6 AND ANTAGONIST?
L8          319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9          140 S L8 AND ANTAGONIST?/CLM
L10          61 S L9 AND AY<2002

=> s l10 and (HIV or human immunodeficiency virus)
         46991 HIV
        538456 HUMAN
         26501 IMMUNODEFICIENCY
        109295 VIRUS
         18871 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L11           4 L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l11,cbib,clm,1-4

L11  ANSWER 1 OF 4  USPATFULL on STN
2004:70745 Substituted 1,3-thiazole compounds, their production and use.
    Ohkawa, Shigenori, Takatsuki-shi, JAPAN
    Naruo, Ken-ichi, Sanda-shi, JAPAN
    Miwatashi, Seiji, Ikeda-shi, JAPAN
    Kimura, Hiroyuki, Sakai-shi, JAPAN
    US 2004053973 A1 20040318
    APPLICATION: US 2002-239692  A1  20020925 (10)
    WO 2001-JP2629 20010329
    PRIORITY: JP 2000-97876  20000330
    JP 2002-2001027571  20020202
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A 1,3-thiazole compound of which 5-position is substituted with a
       4-pyridyl group having a substituent including no aromatic group,
       provided that the 1,3-thiazole compound is not N-[4-(3,5-dimethylphenyl)-
       5-(2-hydroxy-4-pyridyl)-1,3-thiazol-2-yl]acetamide or
       4-(2-(acetylamino)-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]-2-pyridyl
       acetate, or a salt thereof.

       2. A compound as claimed in claim 1 which is a compound represented by
       the formula:   ##STR642## wherein R1 represents a hydrogen atom, a
       hydrocarbon group optionally having a substituent, a heterocyclic group
       optionally having a substituent, an amino group optionally having a
       substituent or an acyl group, R2 represents a 4-pyridyl group
       having a substituent including no aromatic group, and R3 represents
       an aromatic group optionally having a substituent, or a salt thereof.

       3. A 1,3-thiazole compound of which 5-position is substituted with a
       pyridyl group having a substituent including no aromatic group, at a
       position adjacent to a nitrogen atom of the pyridyl group, provided that
       the 1,3-thiazole compound is not N-[4-(3,5-dimethylphenyl)-5-(2-hydroxy-
       4-pyridyl)-1,3-thiazol-2-yl]acetamide or 4-[2-(acetylamino)-4-(3,5-
       dimethylphenyl)-1,3-thiazol-5-yl]-2-pyridyl acetate, or a salt thereof.

       4. A compound of claim 3 which is a compound represented by the formula:
       ##STR643## wherein R1a represents a hydrogen atom, a hydrocarbon
       group optionally having a substituent, a heterocyclic group optionally
       having a substituent, an amino group optionally having a substituent or
       an acyl group, R2a represents a 4-pyridyl group having a
       substituent including no aromatic group, at a position adjacent to a
       nitrogen atom of the pyridyl group, and R3a represents an aromatic
       group optionally having a substituent, or a salt thereof.

       5. A 1,3-thiazole compound of which 5-position is substituted with a
       4-pyridyl group having a substituent including no aromatic group, at a
       position adjacent to a nitrogen atom of the 4-pyridyl group, provided
```

that the 1,3-thiazole compound is not N-[4-(3,5-dimethylphenyl)-5-(2-hydroxy-4-pyridyl)-1,3-thiazol-2-yl]acetamide or 4-[2-(acetylamino)-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]-2-pyridyl acetate, or a salt thereof.

6. A compound as claimed in any one of claims 1 to 5 wherein the substituent including no aromatic group is a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{2-6} alkenyl which may be halogenated, carboxy C_{2-6} alkenyl, C_{2-6} alkynyl which may be halogenated, C_{3-8} cycloalkyl which may be halogenated, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{1-8} alkoxy which may be halogenated, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, hydroxy, mercapto, C_{1-6} alkylthio which may be halogenated, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, di-C_{6-14} arylamino, C_{3-8} cycloalkylamino, C_{3-8} cycloalkyl-C_{1-6} alkylamino, N--C_{3-8} cycloalkyl-N--C_{1-6} alkylamino, formyl, carboxy, carboxy-C_{2-6} alkenyl, carboxy-C_{1-6} alkyl, C_{1-6} alkyl-carbonyl which may be halogenated, C_{3-8} cycloalkyl-carbonyl optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl, carbamoyl, thiocarbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, formylamino, C_{1-6} alkyl-carbonylamino, C_{3-8} cycloalkyl-carbonylamino which may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy-carbonylamino, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, 5- to 7-membered aliphatic heterocyclic group optionally containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to one nitrogen atom and carbon atoms (this aliphatic heterocyclic group optionally has a substituent selected from C_{1-6} alkyl, C_{1-6} alkyl-carbonyl and oxo), sulfo, sulfamoyl, sulfinamoyl, sulfenamoyl or a group obtained by connecting 2 to 3 of these substituents.

7. A compound as claimed in claim 2 or 4 wherein (1) the hydrocarbon group optionally having a substituent is a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-8} cycloalkyl group, a C_{6-14} aryl group or a C_{7-16} aralkyl group, optionally having a substituent selected from Group A of substituents consisting of oxo, a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{2-6} alkenyl which may be halogenated, carboxy C_{2-6} alkenyl, C_{2-6} alkynyl which may be halogenated, C_{3-8} cycloalkyl which may be halogenated, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{6-14} aryl, C_{1-8} alkoxy which may be halogenated, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, hydroxy, C_{6-14} aryloxy, C_{7-16} aralkyloxy, mercapto, C_{1-6} alkylthio which may be halogenated, C_{6-14} arylthio, C_{7-16} aralkylthio, amino, mono-C_{1-6} alkylamino, mono-C_{6-14} arylamino, di-C_{1-6} alkylamino, di-C_{6-14} arylamino, C_{3-8} cycloalkylamino, di-C_{6-14} arylamino, C_{3-8} cycloalkyl-C_{1-6} alkylamino, N--C_{3-8} cycloalkyl-N--C_{1-6} alkylamino, formyl, carboxy, C_{1-6} alkyl-carbonyl which may be halogenated, C_{3-8} cycloalkyl-carbonyl optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{6-14} aryloxy-carbonyl, C_{7-16} aralkyloxy-carbonyl, 5- to 7-membered heterocyclic carbonyl containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, carbamoyl, thiocarbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, mono-C_{6-14} aryl-carbamoyl, di-C_{6-14} aryl-carbamoyl, 5- to 7-membered heterocyclic carbamoyl containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl, C_{1-6} alkylsulfinyl, C_{6-14} arylsulfinyl, formylamino, C_{1-6} alkyl-carbonylamino, C_{3-8} cycloalkyl-carbonylamino optionally substituted by C_{1-6} alkyl, C_{6-14} aryl-carbonylamino, C_{1-6} alkoxy-carbonylamino, C_{1-6} alkylsulfonylamino, C_{6-14} arylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{6-14} aryl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkyl-carbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, mono-C_{6-14} aryl-carbamoyloxy, di-C_{6-14} aryl-carbamoyloxy, nicotinoyloxy, isonicotinoyloxy, 5- to 10-membered

heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms (this heterocyclic group optionally has a substituent selected from C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl which may be halogenated, 5- to 10-membered aromatic heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms and oxo), sulfo, sulfamoyl, sulfinamoyl, sulfenamoyl and a group formed by connecting 2 to 3 of these substituents, (2) the heterocyclic group optionally having a substituent is a 5- to 14-membered heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, which optionally has a substituent selected from Group A of substituents, (3) the acyl group is an acyl group of the formula: --(C.dbd.O)--R, --(C.dbd.O)--OR^{5a}, --(C.dbd.O)--$NR^{5a}R^{6a}$, --(C.dbd.S)--NHR^{5a}, --(C.dbd.O)--$N(OR^{5a})R^{6a}$, --(C.dbd.S)--$NHOR^{5a}$ or --SO_2--R^{7a} (wherein R^{5a} represents {circle over (1)} a hydrogen atom, {circle over (2)} a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-8} cycloalkyl group, a C_{6-14} aryl group or a C_{7-16} aralkyl group, optionally having a substituent selected from Group A of substituents, or {circle over (3)} a 5- to 14-membered heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, which optionally has a substituent selected from Group A of substituents, R^{6a} represents a hydrogen atom or a C_{1-6} alkyl group, and R^{7a} represents {circle over (1)} a C_{1-6} alkyl group, a C_{2-6} alkenylgroup, a C_{2-6} alkynyl group, a C_{3-8} cycloalkyl group, a C_{6-14} aryl group or a C_{7-16} aralkyl group, optionally having a substituent selected from Group A of substituents, or {circle over (2)} a 5- to 14-membered heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, which optionally has a substituent selected from Group A of substituents), (4) the amino group optionally having a substituent is (i) an amino group optionally having 1 or 2 substituents selected from the group consisting of {circle over (1)} a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-8} cycloalkyl group, a C_{6-14} aryl group and a C_{7-16} aralkyl group, optionally having a substituent selected from Group A of substituents, {circle over (2)} a 5- to 14-membered heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, which optionally have a substituent selected from Group A of substituents, {circle over (3)} an acyl group of the formula: --(C.dbd.O)--R^{5a}, --(C.dbd.O)--OR^{5a}, --(C.dbd.O)--$NR^{5a}R^{6a}$, --(C.dbd.S)--NHR^{5a}, --(C.dbd.O)--$N(OR^{5a})R^{6a}$, --(C.dbd.S)--$NHOR^{5a}$ or --SO_2--R^{7a} (wherein each symbol is as defined above), and {circle over (4)} a C_{1-6} alkylidene group optionally having a substituent selected from Group A of substituents, or (ii) a 5- to 7-membered aliphatic cyclic amino group optionally containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to one nitrogen atom and carbon atoms, which optionally has a substituent selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl which may be halogenated, C_{1-6} alkoxy-carbonyl, 5- to 10-membered aromatic heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, and oxo, (5) the substituent containing no aromatic group is a halogen atom, C_{1-3} alkylenedioxy, nitro, cyano, C_{1-6} alkyl which may be halogenated, C_{2-6} alkenyl which may be halogenated, carboxy C_{2-6} alkenyl, C_{2-6} alkynyl which may be halogenated, C_{3-8} cycloalkyl which may be halogenated, C_{3-8} cycloalkyl-C_{1-6} alkyl, C_{1-8} alkoxy which may be halogenated, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, hydroxy, mercapto, C_{1-6} alkylthio which may be halogenated, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, C_{3-8}cycloalkylamino, C_{3-8} cycloalkyl-C_{1-6} alkylamino, N--C_{3-8} cycloalkyl-N--C_{1-6} alkylamino, formyl, carboxy, carboxy-C_{2-6} alkenyl, carboxy-C_{1-6} alkyl, C_{1-6} alkyl-carbonyl which may be halogenated, C_{3-8} cycloalkyl-carbonyl optionally substituted by

C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl, carbamoyl, thiocarbamoyl, mono-C_{1-6} alkyl-carbamoyl, di-C_{1-6} alkyl-carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, formylamino, C_{1-6} alkyl-carbonylamino, C_{3-8} cycloalkyl-carbonylamino which may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy-carbonylamino, C_{1-6} alkylsulfonylamino, C_{1-6} alkyl-carbonyloxy, C_{1-6} alkoxy-carbonyloxy, mono-C_{1-6} alkylcarbamoyloxy, di-C_{1-6} alkyl-carbamoyloxy, 5- to 7-membered aliphatic heterocyclic group optionally containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms (this aliphatic heterocyclic group optionally has a substituent selected from C_{1-6} alkyl, C_{1-6} alkyl-carbonyl and oxo), sulfo, sulfamoyl, sulfinamoyl, sulfenamoyl or a group obtained by connecting 2 to 3 of these substituents, (6) the aromatic group optionally having a substituent is {circle over (1)} a C_{6-14} mono-cyclic or fused poly-cyclic aromatic hydrocarbon group optionally having a substituent selected from Group A of substituents, or {circle over (2)} a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms.

8. A compound as claimed in claim 2 or 4 wherein R^1 represents (i) a hydrogen atom, (ii) a C_{1-6} alkyl group optionally substituted by a substituent selected from the group consisting of a halogen atom, C_{1-6} alkoxy-carbonyl, carboxy, cyano, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, hydroxy, C_{1-6} alkoxy and C_{1-6} alkyl-carbonyl, (iii) a C_{6-14} aryl group optionally having a substituent selected from the group consisting of a halogen atom and a group of the formula: $--S(O)_n--R^{1bb}$ (wherein R^{1bb} represents a C_{1-6} alkyl group, and n represents an integer of 0 to 2), (iv) a C_{7-15} aralkyl group, (v) an amino group optionally having one or two substituents selected from {circle over (1)} C_{1-6} alkyl, {circle over (2)} C_{1-6} alkyl-carbonyl, {circle over (3)} 5- to 7-membered heterocyclic-carbonyl containing 1 to 4 hetero atoms selected from the group-consisting of a nitrogen atom, an oxygen atom and a sulfur atom, in addition to carbon atoms, optionally substituted with a halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy, {circle over (4)} C_{6-14} aryl-carbamoyl, {circle over (5)} C_{1-6} alkyl-carbamoyl which may be halogenated, {circle over (6)} C_{1-6} alkoxy-carbonyl which may be halogenated, {circle over (7)} C_{1-6} alkoxy-carbamoyl and {circle over (8)} C_{6-14} aryloxy-carbamoyl, (vi) a 5- to 10-membered heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, optionally substituted by oxo, C_{1-6} alkyl, C_{6-14} aryl or C_{1-6} alkoxy-carbonyl, (vii) an acyl group represented by the formula: $--(C.dbd.O)--R^{5b}$ (wherein R^{5b} represents a hydrogen atom, a C_{1-6} alkyl group which may be halogenated or a C_{6-14} aryl group which may be halogenated), or (viii) an acyl group represened by the formula: $--(C.dbd.O)--OR^{5c}$ (wherein R^{5c} represents a hydrogen atom or a C_{1-6} alkyl group).

9. A compound as claimed in claim 2 or 4 wherein the substituent having no aromatic group is (1) a C_{1-6} alkyl group (this C_{1-6} alkyl may be substituted by a halogen atom, cyano, hydroxy, or 5- to 6-membered aliphatic heterocyclic group optionally containing hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms), (2) a halogen atom, (3) an amino group optionally having a substituent selected from the group consisting of the following {circle over (1)} to {circle over (7)}; {circle over (1)} a C_{1-6} alkyl group (this C_{1-6} alkyl group may be substituted by a halogen atom, cyano, hydroxy, C_{3-8} cycloalkyl or 5- to 7-membered aliphatic heterocyclic group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms), {circle over (2)} C_{3-8} cycloalkyl group, {circle over (3)} a C_{1-6} alkyl-carbonyl group (this C_{1-6} alkyl-carbonyl group maybe substituted by a halogen atom, cyano, hydroxy, C_{3-8} cycloalkyl or 5- to 7-membered aliphatic heterocyclic group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms), {circle over (4)} a C_{1-6} alkoxy-carbonyl group, {circle over (5)} a C_{3-8} cycloalkyl-carbonyl group optionally substituted by C_{1-6} alkyl, {circle over (6)} a 5- to 6-membered aliphatic

heterocyclic group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms (this aliphatic heterocyclic group may be substituted by C_{1-6} alkyl or C_{1-6} alkyl-carbonyl), {circle over (7)} a 5- to 6-membered aliphatic heterocyclic-carbonyl group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms (this aliphatic heterocyclic-carbonyl group may be substituted by C_{1-6} alkyl or C_{1-6} alkyl-carbonyl), (4) a 5- to 7-membered aliphatic cyclic amino group optionally further containing hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms and one nitrogen atom (this aliphatic cyclic amino group may be substituted by C_{1-6} alkyl or C_{1-6} alkyl-carbonyl), (5) a hydroxy group, or (6) a C_{1-6} alkyl-carbonyloxy group.

10. A compound as claimed in claim 2 or 4 wherein R^3 is {circle over (1)} a C_{6-14} aryl group or {circle over (2)} a 5- to 14-membered aromatic heterocyclic group preferably containing 1 to 4 of 1 or 2 kinds of hatero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, which optionally has substituents selected from the group consisting of C_{1-6} alkyl which may be halogenated, C_{1-6} alkoxy, a halogen atom, carboxyl, C_{1-6} alkoxy-carbonyl, cyano, C_{1-6} alkylthio and C_{1-6} alkylsulfonyl.

11. A compound as claimed in claim 3 which is a compound of the formula: ##STR644## wherein R^{1b} represents (i) a hydrogen atom, (ii) a C_{1-6} alkyl group optionally substituted by a substituent selected from the group consisting of a halogen atom, C_{1-6} alkoxy-carbonyl, carboxy, cyano, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, hydroxy, C_{1-6} alkoxy and C_{1-6} alkyl-carbonyl, (iii) a C_{6-14} aryl group optionally having a substituent selected from the group consisting of a halogen atom and a group of the formula: $--S(O)_n--R^{1bb}$ (R^{1bb} represents a C_{1-6} alkyl group, and n represents an integer of 0 to 2), (iv) a C_{7-15} aralkyl group, (v) an amino group optionally having one or two substituents selected from {circle over (1)} C_{1-6} alkyl, {circle over (2)} C_{1-6} alkyl-carbonyl, {circle over (3)} C_{1-6} alkyl-carbonyl, {circle over (4)} 5- to 7-membered heterocyclic-carbonyl containing 1 to 4 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms, optionally substituted with a halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy, {circle over (4)} C_{6-14} aryl-carbamoyl, {circle over (5)} C_{1-6} alkyl-carbamoyl which may be halogenated, {circle over (6)} C_{1-6} alkoxy-carbonyl which may be halogenated, {circle over (7)} C_{1-6} alkoxy-carbamoyl and {circle over (8)} C_{6-14} aryloxy-carbamoyl, (vi) a 5- to 10-membered heterocyclic group containing 1 to 4 of 1 or 2 kinds of hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, optionally substituted by oxo, C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl or C_{1-6} alkoxy-carbonyl, (vii) an acyl group represented by the formula: $--(C.dbd.O)--R^{5b}$ (wherein R^{5b} represents a hydrogen atom, a C_{1-6} alkyl group which may be halogenated or a C_{6-14} aryl group which may be halogenated), or (viii) an acyl group represented by the formula: $--(C.dbd.O)--OR^{5c}$ (wherein R^{5c} represents a hydrogen atom or C_{1-6} alkyl group), R^{2b} represents a pyridyl group having at the position adjacent to a nitrogen atom of the pyridyl group a substituent selected from the group consisting of (1) a C_{1-6} alkyl group (this C_{1-6} alkyl group may be substituted by a halogen atom, cyano, hydroxy, or a 5- to 7-membered aliphatic heterocyclic group optionally containing hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms), (2) a halogen atom, (3) an amino group optionally having a substituent selected from the group consisting of the following {circle over (1)} to {circle over (7)}; {circle over (1)} a C_{1-6} alkyl group (this C_{1-6} alkyl group may be substituted by a halogen atom, cyano, hydroxy, C_{3-8} cycloalkyl or a 5- to 7-membered aliphatic heterocyclic group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms), {circle over (2)} a C_{3-8} cycloalkyl group, {circle over (3)} a C_{1-6} alkyl-carbonyl group (this C_{1-6} alkyl-carbonyl group may be substituted by a halogen atom, cyano, hydroxy, C_{3-8} cycloalkyl or a 5- to 7-membered aliphatic

heterocyclic group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms), {circle over (4)} a C_{1-6} alkoxy-carbonyl group, {circle over (5)} a C_{3-8} cycloalkyl-carbonyl group optionally substituted by C_{1-6} alkyl, {circle over (6)} a 5- to 7-membered aliphatic heterocyclic group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms (this aliphatic heterocyclic group may be substituted by C_{1-6} alkyl or C_{1-6} alkyl-carbonyl), {circle over (7)} a 5- to 7-membered aliphatic heterocyclic-carbonyl group optionally having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms (this aliphatic heterocyclic-carbonyl group may be substituted by C_{1-6} alkyl or C_{1-6} alkyl-carbonyl), (4) a 5- to 7-membered aliphatic cyclic amino group optionally further containing hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom in addition to carbon atoms and one nitrogen atom (this saturated cyclic amino group may be substituted by C_{1-6} alkyl or C_{1-6} alkyl-carbonyl), (5) a hydroxy group, and (6) a C_{1-6} alkyl-carbonyloxy group, and R^{3b} represents {circle over (1)} a C_{6-14} aryl group or {circle over (2)} a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 of 1 or 2 kinds of hatero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom in addition to carbon atoms, which optionally has a substituent selected from the group consisting of C_{1-6} alkyl which may be halogenated, C_{1-6} alkoxy, a halogen atom, carboxyl, C_{1-6} alkoxy-carbonyl, cyano, C_{1-6} alkylthio and C_{1-6} alkylsulfonyl, or a salt thereof.

12. A compound as defined in [11] wherein the pyridyl group is a 4-pyridyl group.

13. A compound as defined in [11] wherein R^{1b} is a C_{1-6} alkyl group optionally having a substituent selected from the group consisting of a halogen atom, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl and C_{1-6} alkylsulfonyl, R^{2b} is a 4-pyridyl group having a C_{1-6} alkyl-carbonyl-amino group or a C_{3-8} cycloalkylamino group at the position adjacent to a nitrogen atom of the 4-pyridyl group, R^{3b} is a C_{6-14} aryl group which optionally has a substituent selected from the group consisting of C_{1-6} alkyl and a halogen atom.

14. A compound as defined in [11] wherein R^{1b} is a C_{1-3} alkyl group optionally having a substituent selected from the group consisting of a halogen atom, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl and C_{1-6} alkylsulfonyl, R^{2b} is a 4-pyridyl group having a C_{1-3} alkyl-carbonyl-amino group or a C_{3-8} cycloalkylamino group at the position adjacent to a nitrogen atom of the 4-pyridyl group, R^{3b} is a phenyl group which optionally has a substituent selected from the group consisting of methyl and a chlorine atom.

15. A compound as claimed in claim 5 which is 5-[2-(tert-butoxycarbonylamino)-4-pyridyl]-2-ethyl-4-(3-methylphenyl)-1,3-thiazole, [4-(3-methylphenyl)-5-(2-methyl-4-pyridyl)-1,3-thiazol-2-yl]amine, 2-ethyl-5-(2-fluoro-4-pyridyl)-4-(3-methylphenyl)-1,3-thiazole, 5-(2-fluoro-4-pyridyl)-4-(3-methylphenyl)-2-[4-(methylthio)phenyl]-1,3-thiazole, 4-(3-methylphenyl)-5-(2-methyl-4-pyridyl)-2-[4-(methylthio)phenyl]-1,3-thiazole, 4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine, N-[4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]acetamide, N-[4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]propionamide, N-[4-[4-(3-chlorophenyl)-2-methyl-1,3-thiazol-5-yl]-2-pyridyl]acetamide, N-[4-[4-(3-chlorophenyl)-2-ethyl-1,3-thiazol-5-yl]-2-pyridyl]acetamide, N-[4-[4-(3-chlorophenyl)-2-propyl-1,3-thiazol-5-yl]-2-pyridyl]acetamide, N-[4-[4-(3-chlorophenyl)-2-methyl-1,3-thiazol-5-yl]-2-pyridyl]propionamide, N-[4-[4-(3-chlorophenyl)-2-ethyl-1,3-thiazol-5-yl]-2-pyridyl]propionamide, N-[4-[4-(3-chlorophenyl)-2-propyl-1,3-thiazol-5-yl]-2-pyridyl]propionamide, N-cyclohexyl-4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine, N-cyclohexyl-4-[4-(3-methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine, N-cyclopentyl-4-[-2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine, N-cyclopentyl-4-[4-(3-methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridylamine, 4-[4-(3-chlorophenyl)-2-ethyl-1,3-thiazol-5-yl]-N-cyclohexyl-2-

pyridylamine, 4-[4-(3-chlorophenyl)-2-ethyl-1,3-thiazol-5-yl]-N-cyclopentyl-2-pyridylamine, N-[4-(3-methylphenyl)-5-(2-methyl-4-pyridyl)-1,3-thiazol-2-yl]acetamide, N-[4-(3,5-dimethylphenyl)-5-(2-methyl-4-pyridyl)-1,3-thiazol-2-yl]nicotinamide, 6-chloro-N-[4-(3,5-dimethylphenyl)-5-(2-methyl-4-pyridyl)-1,3-thiazol-2-yl]nicotinamide, N-[4-(3,5-dimethylphenyl)-5-(2-methyl-4-pyridyl)-1,3-thiazol-2-yl]-6-methylnicotinamide, N-[4-(3,5-dimethylphenyl)-5-(2-methyl-4-pyridyl)-1,3-thiazol-2-yl]-6-methoxynicotinamide, 4-(3-methylphenyl)-5-(2-methyl-4-pyridyl)-2-(4-methylsulfinylphenyl)-1,3-thiazole, 4-(3-methylphenyl)-5-(2-methyl-4-pyridyl)-2-(4-methylsulfonylphenyl)-1,3-thiazole, 5-(2-fluoro-4-pyridyl)-4-(3-methylphenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazole, N-[4-[4-(3-chlorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]acetamide, N-[4-[4-(3-chlorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]propionamide, N-[4-[4-(3-chlorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazol-5-yl]-2-pyridyl]pivalamide, or a salt thereof.

16. A pro-drug of a compound as claimed in any one of claims 1 to 5.

17. A method for producing a compound as claimed in claim 2 or 4 comprising (1) reacting a compound represented by the formula: ##STR645## wherein Hal represents a halogen atom, R^2 and R^3 are as defined in claim 2, or a salt thereof with a compound of the formula: ##STR646## wherein R^1 is as defined in claim 2, or a salt thereof, or (2) reacting a compound represented by the formula: ##STR647## wherein Hal represents a halogen atom, R^{2a} and R^{3a} are as defined in claim 4, or a salt thereof with a compound represented by the formula: ##STR648## wherein R^{1a} is as defined in claim 4, or a salt thereof.

18. A pharmaceutical composition containing the compound as claimed in any one of claims 1 to 5 or a prodrug thereof.

19. The composition as claimed in claim 18 which is a p38 MAP kinase inhibitor.

20. The composition as claimed in claim 18 which is a TNF-α production inhibitor.

21. The composition as claimed in claim 18 which is a composition for preventing or treating a cytokine-madiated disease.

22. The composition as claimed in claim 18 which is an **adenosine receptor antagonist**.

23. The composition as claimed in claim 18 which is a composition for preventing or treating **adenosine receptor**-mediated diseases.

24. The composition as claimed in claim 18 which is a composition for preventing or treating asthma or allergic diseases.

25. The composition as claimed in claim 18 which is a composition for preventing or treating inflammation, Addison's disease, autoimmune hemolytic anemia, Crohn's disease, psoriasis, rheumatism, spinal cord injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, diabetes, arthritis, toxaemias, ulcerative colitis, chronic pneumonia, pulmonary silicosis, pulmonary sarcoidosis, lung tuberculosis, cachexia, arterial sclerosis, Creutzfeldt-Jakob disease, virus infection, atopic dermatitis, systemic lupus erythematosus, AIDS encephalopathy, meningitis, angina-pectoris, myocardial infarction, congestive heart failure, hepatitis, transplant, dialysis hypotension or diffuse intravascular coagulation symdrome.

26. The composition as claimed in claim 18 which is a composition for preventing or treating chronic rheumatoid arthritis or osteoarthritis.

27. The composition as claimed in claim 18 which is a composition for preventing or treating cerebral edema, cerebrovascular disorder, head trauma, cerebral infarction or apoplectic stroke.

28. A method for inhibiting p38 MAP kinase which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

29. A method for inhibiting TNF-α production which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

30. A method for antagonizing an **adenosine receptor** which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

31. A method for preventing or treating asthma or allergic diseases which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

32. A method for preventing or treating inflammation, Addison's disease, autoimmune hemolytic anemia, Crohn's disease, psoriasis, rheumatism, spinal cord injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, diabetes, arthritis, toxaemias, ulcerative colitis, chronic pneumonia, pulmonary silicosis, pulmonary sarcoidosis, lung tuberculosis, cachexia, arterial sclerosis, Creutzfeldt-Jakob disease, virus infection, atopic dermatitis, systemic lupus erythematosus, AIDS encephalopathy, meningitis, angina pectoris, myocardial infarction, congestive heart failure, hepatitis, transplant, dialysis hypotension or diffuse intravascular coagulation symdrome which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

33. A method for preventing or treating chronic rheumatoid arthritis or osteoarthritis which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

34. A method for preventing or treating cerebral edema, cerebrovascular disorder, head trauma, cerebral infarction or apoplectic stroke which comprises administering an effective amount of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof to mammals.

35. Use of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof for producing a p38 MAP kinase inhibitor.

36. Use of the compound as claimed in any one of claims 1 to 5 or pro-drug thereof for producing a TNF-α production inhibitor.

37. Use of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof for producing an adnosine receptor antoganist.

38. Use of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof for producing a composition for preventing or treating asthma and allergic diseases.

39. Use of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof for producing a composition for preventing or treating inflammation, Addison's disease, autoimmune hemolytic anemia, Crohn's disease, psoriasis, rheumatism, spinal cord injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, diabetes, arthritis, toxaemias, ulcerative colitis, chronic pneumonia, pulmonary silicosis, pulmonary sarcoidosis, lung tuberculosis, cachexia, arterial sclerosis, Creutzfeldt-Jakob disease, virus infection, atopic dermatitis, systemic lupus erythematosus, AIDS encephalopathy, meningitis, angina pectoris, myocardial infarction, congestive heart failure, hepatitis, transplant, dialysis hypotension or diffuse intravascular coagulation symdrome.

40. Use of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof for producing a composition for preventing or treating chronic rheumatoid arthritis or osteoarthritis.

41. Use of the compound as claimed in any one of claims 1 to 5 or a pro-drug thereof for producing a composition for preventing or treating cerebral edema, cerebrovascular disorder, head trauma, cerebral infarction or apoplectic stroke.

L11 ANSWER 2 OF 4 USPATFULL on STN
2003:306976 Methanocarba cycloakyl nucleoside analogues.
Jacobson, kenneth A, Silver Spring, MD, UNITED STATES
Marquez, Victor E, Montgomery, MD, UNITED STATES

US 2003216412 A1 20031120
APPLICATION: US 2002-169975 A1 20020712 (10)
WO 2001-US981 20010112
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A compound having the formula A-M, wherein A is a chemically modified adenine or uracil and M is a constrained cycloalkyl group, said adenine or uracil is bonded to said constrained cycloalkyl group, and said compound binds a receptor; or a salt of said compound.

2. The compound of claim 1, wherein said receptor is a P1 or P2 receptor.

3. The compound of claim 2, wherein said P1 receptor is selected from the group consisting of A_1,A_{2A}, and A_3.

4. The compound of claim 2, wherein said P2 receptor is selected from the group consisting of P2Y and P2X.

5. The compound of claim 1, wherein said constrained cycloalkyl group includes a cyclopentyl group.

6. The compound of claim 3, wherein said constrained cyclopentyl group is a cyclopentyl ring derivatized with a fused cyclopropane bridge.

7. The compound of claim 1, wherein said constrained cycloalkyl group is constrained in the N-conformation.

8. The compound of claim 1, wherein said constrained cycloalkyl group is constrained in the S-conformation.

9. A compound selected from the group consisting of ##STR15## wherein R_1 is hydrogen, alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, arylalkyl, acyl, sulfonyl, arylsulfonyl, thiazolyl or bicyclic alkyl; R_2 is hydrogen, halo, alkyl, aryl, arylamino, aryloxide, alkynyl, alkenyl, thiol, cyano, or; R_3, R_4, and R_5, are each independently hydrogen, hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, aryl, acyl, alkylamino, arylamino, phosphoryl, diphosphoryl, triphosphoryl, phosphonyl, boronyl, thiophosphoryl, thiodiphosphoryl, thiotriphosphoryl or vanadyl, and can be the same or different; R_6 is hydrogen, alkyl, alkenyl, alkynyl, heteroaryl or aminoalkyl; R_7 is methylene, dihalomethyl, carbonyl, sulfoxide; and at least one of R_1, R_2, and R_6 is other than hydrogen; R_8 is carbon or nitrogen; or a salt of said compound.

10. The compound of claim 9, wherein R_1 is alkyl, cycloalkyl, alkoxy, aryl, arylalkyl, bicycloalkyl, or sulfonyl.

11. The compound of claim 9, wherein R_1 is methyl, cyclopentyl, cyclohexyl, phenyl, R-phenylisopropyl, benzyl, or phenylethyl; R_2 is chloro; and R_6 is C_{1-C6} alkylamino, C_{1-C6} alkyl, C_{2-C6} alkenyl, C_{2-C6} alkynyl.

12. The compound of claim 9 or 10, wherein R_1 is further substituted with a member selected from the group consisting of hydroxyl, halo, sulfonyl, amino, cyano, alkoxyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, sulfonamido, carboxyl, and carboxamido.

13. The compound of claim 9, wherein R_1 is methyl group and R_2 is chloro, alkyithio, or arylalkylthio.

14. The compound of claim 9, wherein R_6 is methyl and R_2 is chloro, alkylthio, arylalkylthio or hydrogen.

15. The compound of claim 9, wherein R_6 is halo and R_2 is a chloro, alkylthio, arylalkylthio or hydrogen.

16. The compound of claim 9, wherein R_2 is chloro.

17. The compound of claim 9, wherein R_1 is methyl and R_2 is chloro and R_3 is hydrogen.

18. The compound of claim 9, wherein the compound has the formula ##STR16## wherein R_1 is iodobenzyl, or cyclopentyl and R_2 is hydrogen or chloro.

19. The compound of claim 9, wherein the compound has the formula ##STR17##

20. The compound of claim 9, wherein the compound has the formula ##STR18##

21. A compound selected from the group consisting of: ##STR19## wherein R_1, R_2, R_9 is hydrogen, alkyl, alkenyl, alkynyl, aminoalkyl and R_3, R_4, and R_5, are each independently hydrogen, hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, aryl, acyl, alkylamino, arylamino, phosphoryl, phosphonyl, boronyl, or vanadyl, and can be the same or different; R_6 and R_7 are each independently sulfur or oxygen; and R_{10} is methylene, dihalomethyl, carbonyl, sulfoxide; or a salt of said compound.

22. The compound of claim 21, wherein R_1 is methyl.

23. A compound comprising a methanocarbocyclic analog of a chemically modified adenosine or uradine wherein said compound is a P2 receptor ligand; or a salt of said compound.

24. The compound of claim 23, wherein the compound is a P2 receptor agonist.

25. The compound of claim 23, wherein the compound is a P2 receptor **antagonist**.

26. The compound of claim 22, wherein said P2 receptor is selected from the group consisting of P2Y and P2X.

27. The compound of claim 22, wherein said P2 receptor is a P2Y receptor.

28. The compound of claim 22, wherein said P2 receptor is a P2Y1 receptor.

29. The compound of claim 22, wherein said P2 receptor is a **P2X receptor**.

30. A compound comprising a methanocarbocyclic analog of a chemically modified adenosine or uradine wherein said compound is a P1 receptor ligand; or a salt of said compound.

31. The compound of claim 30, wherein the compound is a P1 receptor agonist.

32. The compound of claim 30, wherein the compound is a P1 receptor **antagonist**.

33. The compound of claim 30, wherein said P1 receptor is selected from the group consisting of A_1,A_{2A}, and A_3.

34. The compound of claim 30, wherein said P1 receptor is A_1 receptor.

35. The compound of claim 30, wherein said P1 receptor is A_3 receptor.

36. A method of treating or preventing in a mammal a disease, state, or condition that responds to an adenosine, ATP, or UTP receptor agonist or **antagonist** comprising administering to the mammal a compound of any of any of claims 1-36.

37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 1-36.

33. The use of a compound of any of claims 1-36 as a medicament.

34. The use of a methanocarba analog in the manufacture of a medicament for the treatment or prevention in a mammal a disease state, or

condition that responds to an adenosine, ATP, UTP receptor agonist or **antagonist**.

35. A method for the treatment of airway diseases, cancer, cardiac arrhythmia, cardiac ischemia, epilepsy, Huntington's Disease, immunodeficient disorders, inflammatory disorders, neonatal hypoxia, neurodegenerative, pain, Parkinson's Disease, renal failure, schizophrenia, sleep disorders, stroke, thrombosis, urinary incontinence, diabetes, psoriasis, septic shock, brain trauma, glaucoma, or congestive heart failure in individuals in need of such treatment comprising contacting an effective quantity of a compound of any of claims 1-36.

L11 ANSWER 3 OF 4 USPATFULL on STN
2002:17300 TNFalpha **antagonists** and methotrexate in the treatment of TNF-mediated disease.
Feldmann, Marc, London, UNITED KINGDOM
Maini, Ravinder N., London, UNITED KINGDOM
The Kennedy Institute of Rheumatology, England (non-U.S. corporation)
US 2002010180 A1 20020124
APPLICATION: US 2001-754004 A1 20010103 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for treating or preventing a tumor necrosis factor-mediated disease in an individual in need thereof comprising co-administering methotrexate and a TNFα **antagonist** to said individual, in therapeutically effective amounts.

2. A method of claim 1 wherein said TNFα **antagonist** and methotrexate are administered simultaneously.

3. A method of claim 1 wherein said TNFα **antagonist** and methotrexate are administered sequentially.

4. A method of claim 1 wherein the tumor necrosis factor-mediated disease is selected from the group consisting of: autoimmune disease, acute or chronic immune disease, inflammatory disease and neurodegenerative disease.

5. A method of claim 4 wherein said TNFα **antagonist** is administered in multiple doses.

6. A method of claim 1 wherein said TNFα **antagonist** prevents or inhibits TNFα synthesis or TNFα release.

7. A method of claim 6 wherein said TNFα **antagonist** is a phosphodiesterase inhibitor.

8. A method of claim 7 wherein said phosphodiesterase inhibitor is selected from the group consisting of: pentoxifylline and rolipram.

9. A method of claim 6 wherein said TNFα **antagonist** is selected from the group consisting of: thalidomide and tenidap.

10. A method of claim 6 wherein said TNFα **antagonist** is selected from the group consisting of: a A2b **adenosine receptor** agonist and a A2b **adenosine receptor** enhancer.

11. A method of claim 5 wherein said TNFα **antagonist** is an anti-TNFα antibody or antigen-binding fragment thereof.

12. A method of claim 11 wherein said anti-TNFα antibody or antigen-binding fragment is a chimeric antibody or chimeric fragment, wherein said chimeric antibody or chimeric fragment comprises a non-human variable region specific for TNFα or an antigen-binding portion thereof and a human constant region.

13. A method of claim 12 wherein said chimeric antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

14. A method of claim 13 wherein said chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

15. A method of claim 13 wherein said chimeric antibody is monoclonal antibody cA2.

16. A method of claim 11 wherein said anti-TNFα antibody is a humanized antibody or antigen-binding fragment thereof.

17. A method of claim 16 wherein said humanized antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

18. A method of claim 11 wherein said anti-TNFα antibody is a resurfaced antibody or antigen-binding fragment thereof.

19. A method of claim 18 wherein said resurfaced antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

20. A method of claim 5 wherein said TNFα **antagonist** is a soluble TNFα receptor or functional portion thereof.

21. A method of claim 20 wherein said soluble TNFα receptor is selected from the group consisting of: p55 TNFα receptor and p75 TNFα receptor.

22. A method of claim 20 wherein said soluble TNFα receptor is a TNFα receptor multimeric molecule.

23. A method of claim 20 wherein said soluble TNFα receptor is a TNFα receptor immunoreceptor fusion molecule.

24. A method for treating or preventing arthritis in an individual in need thereof comprising co-administering methotrexate and a TNFα **antagonist** to said individual, in therapeutically effective amounts.

25. A method of claim 24 wherein said TNFα **antagonist** and methotrexate are administered simultaneously.

26. A method of claim 24 wherein said TNFα **antagonist** and methotrexate are administered sequentially.

27. A method of claim 24 wherein said TNFα **antagonist** is administered in multiple doses.

28. A method of claim 24 wherein said TNFα **antagonist** prevents or inhibits TNFα synthesis or TNFα release.

29. A method for treating or preventing rheumatoid arthritis in an individual in need thereof comprising co-administering methotrexate and a TNFα **antagonist** to said individual, in therapeutically effective amounts.

30. A method of claim 29 wherein said TNFα **antagonist** and methotrexate are administered simultaneously.

31. A method of claim 29 wherein said TNFα **antagonist** and methotrexate are administered sequentially.

32. A method of claim 29 wherein said TNFα **antagonist** is administered in multiple doses.

33. A method of claim 29 wherein said TNFα **antagonist** prevents or inhibits TNFα synthesis or TNFα release.

34. A method for treating or preventing Crohn's disease in an individual in need thereof comprising co-administering methotrexate a TNFα **antagonist** to said individual, in therapeutically effective amounts.

35. A method of claim 34 wherein said TNFα **antagonist** and methotrexate are administered simultaneously.

36. A method of claim 34 wherein said TNFα **antagonist** and methotrexate are administered sequentially.

37. A method of claim 34 wherein said TNFα **antagonist** is

administered in multiple doses.

38. A method of claim 34 wherein said TNFα **antagonist** prevents or inhibits TNFα synthesis or TNFα release.

L11 ANSWER 4 OF 4 USPATFULL on STN
2001:90260 Fatty acid-pharmaceutical agent conjugates.
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
Swindell, Charles S., Merion, PA, United States
Shashoua, Victor E., Brookline, MA, United States
US 2001002404 A1 20010531
APPLICATION: US 2000-730450 A1 20001205 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for targeting a pharmaceutical agent to a noncentral nervous system tissue to treat a noncentral nervous system condition comprising: administering to a subject in need of such treatment a covalent conjugate of a C8-26, unbranched, naturally occurring fatty acid and a pharmaceutical agent effective for treating said condition provided that the drug is not an **adenosine receptor** agonist or **antagonist**.

2. The method of claim 1, wherein the tissue is breast tissue and wherein the subject has a condition calling for treatment of breast tissue with the pharmaceutical agent.

3. The method of claim 1, wherein the tissue is gastrointestinal tissue and wherein the subject has a condition calling for treatment of gastrointestinal tissue with the pharmaceutical agent.

4. The method of claim 1, wherein the tissue is ovarian tissue and wherein the subject has a condition calling for treatment of ovarian tissue with the pharmaceutical agent.

5. The method of claim 1, wherein the pharmaceutical agent is a noncentral nervous system active agent that is nonactive within the central nervous system.

6. The method of claim 1, wherein the drug is an anti-cancer agent.

7. The method of claim 1, wherein the fatty acid is selected from the group consisting of C8:0 (caprylic acid), C10:0 (capric acid), C12:0 (lauric acid), C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 (α-linolenic acid), C18:3-5 (eleostearic), C18:3-6 (δ-linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo-y-linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic), C22:6-3 (docosahexaenoic acid) and C24:1-9 (nervonic).

8. The method of claim 1, wherein the fatty acid is selected from the group consisting of C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 (α-linolenic acid), C18:3-5 (eleostearic), C18:3-6 (δ-linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo-y-linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic), and C22:6-3 (docosahexaenoic acid).

9. A pharmaceutical preparation comprising: a covalent conjugate of a C8-C26 uunbranched, naturally occurring fatty acid and a noncentral nervous system active agent, and a pharmaceutically acceptable carrier.

10. The pharmaceutical preparation of claim 9, wherein the fatty acid is selected from the group consisting of C8:0 (caprylic acid), C10:0 (capric acid), C12:0 (lauric acid), C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 (α-linolenic acid), C18:3-5 (eleostearic), C18:3-6

(δ-linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo-y-linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic), C22:6-3 (docosahexaenoic acid) and C24:1-9 (nervonic).

11. The pharmaceutical preparation of claim 9, wherein the fatty acid is selected from the group consisting of C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 (α-linolenic acid), C18:3-5 (eleostearic), C18:3-6 (δ-linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo-y-linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic), and C22:6-3 (docosahexaenoic acid).

12. The pharmaceutical agent of claims 9-11, wherein the noncentral nervous system active agent is active on a tissue selected from the group consisting of: Blood and Blood Forming tissue; Cardiovascular system tissue; Digestive and excretory system tissue; Endocrine system tissue; Musclar system tissue; Reproductive System tissue; Respiratory system tissue; Skeletal system tissue; and Fiber and integumentary system tissue.

```
=> s l10 not l11
L12         57 L10 NOT L11

=> s l12 and (ADA/clm or adenosine deaminase deficiency/clm)
           276 ADA/CLM
          2936 ADENOSINE/CLM
           694 DEAMINASE/CLM
          3632 DEFICIENCY/CLM
            16 ADENOSINE DEAMINASE DEFICIENCY/CLM
                 ((ADENOSINE(W)DEAMINASE(W)DEFICIENCY)/CLM)
L13          1 L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)

=> d l13,cbib,clm

L13  ANSWER 1 OF 1  USPATFULL on STN
2002:166381 Adenosine deaminase deficient transgenic mice and methods for the
    use thereof.
    Kellems, Rodney E., Houston, TX, UNITED STATES
    Datta, Surjit K., Houston, TX, UNITED STATES
    Blackburn, Michael R., Pearland, TX, UNITED STATES
    Board of Regents, The University of Texas System (U.S. corporation)
    US 2002088017 A1 20020704
    APPLICATION: US 2001-761198  A1  20010116 (9)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A mouse comprising a tissue-specific ADA transgene which is
       homozygous for a null Ada allele.

       2. The mouse of claim 1, wherein the tissue-specific ADA transgene is
       expressed at a developmental stage during fetal development.

       3. The mouse of claim 2, wherein the tissue-specific transgene is
       expressed in trophoblasts during development.

       4. The mouse of claim 1, wherein there is substantially no ADA
       activity present in the mouse after birth.

       5. The mouse of claim 4, wherein the tissue-specific transgene is
       expressed in trophoblasts during development.

       6. The mouse of claim 5, wherein the tissue-specific transgene is
       expressed in trophoblasts during development and the mouse exhibits
       ADA expression after birth.

       7. The mouse of claim 1, wherein the ADA activity exhibited after
       birth is the result of expression of an ADA transgene other than the
```

transgene expressed in the trophoblasts during development.

8. A method of producing a mouse that is homozygous for a null **Ada** allele comprising: crossing a first mouse comprising a tissue-specific **ADA** transgene with a second mouse heterozygous for a null **Ada** allele to obtain a third mouse comprising the transgene and the null **Ada** allele; crossing the third mouse with a fourth mouse to produce a fifth mouse that comprises the tissue-specific **ADA** transgene and is homozygous for the null **Ada** allele.

9. The method of claim 8, wherein the tissue-specific **ADA** transgene is expressed at a developmental stage during the fetal development of the fifth mouse.

10. The method of claim 9, wherein the tissue-specific transgene is expressed in trophoblasts during development of the fifth mouse.

11. The method of claim 8, wherein the fourth mouse is heterozygous for a null **Ada** allele.

12. The method of claim 8, wherein the fourth mouse is homozygous for a null **Ada** allele.

13. The method of claim 8, wherein the fourth mouse comprises a tissue-specific **ADA** transgene.

14. A mouse comprising a tissue-specific **ADA** transgene which is homozygous for a null **Ada** allele preparable by: crossing a first mouse comprising a tissue-specific **ADA** transgene with a second mouse heterozygous for a null **Ada** allele to obtain a third mouse comprising the transgene and the null **Ada** allele; crossing the third mouse with a fourth mouse to produce a fifth mouse that comprises the tissue-specific **ADA** transgene and is homozygous for the null **Ada** allele.

15. A method of screening for compounds having pharmaceutical activity in the treatment of a dysfunction indicated by an elevated level of adenosine comprising: obtaining a mouse with a reduced level of **ADA** activity and a dysfunction indicated by an elevated level of adenosine; obtaining a candidate compound; administering the candidate compound to the mouse; monitoring the mouse to determine whether the candidate compound manifests pharmaceutical activity.

16. The method of claim 15, wherein the dysfunction is manifested in the respiratory, nervous, cardiovascular, vascular, renal, skeletal, reproductive, and/or immune systems.

17. The method of claim 16, wherein the dysfunction is manifested in the respiratory system.

18. The method of claim 17, wherein the dysfunction is manifested as asthma.

19. The method of claim 16, wherein the dysfunction is manifested in the immune system.

20. The method of claim 15, wherein the mouse has substantially no **ADA** activity after birth.

21. The method of claim 15, wherein the mouse exhibits **ADA** activity after birth, at a reduced level relative to a normal mouse.

22. The method of claim 15, wherein the mouse is homozygous for a null **Ada** allele.

23. The method of claim 15, wherein the mouse comprises a tissue-specific **ADA** transgene and is homozygous for a null **Ada** allele.

24. The method of claim 23, wherein the tissue-specific **ADA** transgene is expressed in trophoblasts during development.

25. The method of claim 23, wherein the tissue-specific **ADA** transgene is expressed in stomach tissue in the mouse after birth.

26. The method of claim 15, wherein the candidate compound acts through an **adenosine receptor**.

27. The method of claim 26, wherein the candidate compound is an agonist of an **adenosine receptor**.

28. The method of claim 26, wherein the candidate compound is an **antagonist** of an **adenosine receptor**.

29. The method of claim 15, wherein the candidate compound is a polypeptide.

30. The method of claim 29, wherein the polypeptide is an **ADA** polypeptide.

31. The method of claim 15, wherein the candidate compound is an enzyme capable of metabolizng adenosine or 2'-deoxyadenosine.

32. A method of treating a mammal having a dysfunction indicated by an elevated level of adenosine comprising treating the mammal to reduce the level of adenosine relative to the elevated level of adenosine.

33. The method of claim 32, wherein the dysfunction is manifested in the respiratory, nervous, cardiovascular, vascular, renal, skeletal, reproductive, and/or immune systems.

34. The method of claim 33, wherein the dysfunction is manifested in the respiratory system.

35. The method of claim 34, wherein the respiratory dysfunction is manifested as asthma.

36. The method of claim 32, wherein the dysfunction is manifested in the immune system.

37. The method of claim 32, wherein the treatment of the mammal comprises providing **ADA** to the mammal.

38. The method of claim 37, wherein the **ADA** is provided by injection of **ADA** into the mammal.

39. The method of claim 38, wherein the **ADA** is provided at a dosage of 3 to 300 Units per kilogram weight of the mammal.

40. The method of claim 37, wherein the **ADA** is provided in a single introduction procedure.

41. The method of claim 37, wherein the **ADA** is provided by a series of introduction procedures.

42. The method of claim 37, wherein the **ADA** is provided by a series of injections.

43. The method of claim 42, wherein the **ADA** is provided by injections that occur at roughly once or twice weekly intervals.

44. The method of claim 37, wherein the **ADA** is provided by introducing into the mammal a gene encoding **ADA** in a manner that leads to expression of **ADA** in the mammal.

45. The method of claim 37, wherein the **ADA** is provided by placing **ADA**-producing cells in the mammal.

46. The method of claim 37, wherein the **ADA** is provided by injection of **ADA** into the mammal.

47. A method of rescuing an **ADA** deficient fetus which comprises providing one or more tissues of the **ADA** deficient fetus with **ADA**.

48. A method of expressing **ADA** in a tissue of an animal prenatally in a manner in which it is turned off postnatally which comprises providing a placenta specific transgene to said animal.

49. A method of rescuing an **ADA** deficient fetus which comprises providing one or more tissues of the **ADA** deficient fetus with a compound selected from the group consisting of S-adenosylhomocysteine hydrolase, ribonucleotide reductase, caspases, DNA fragmentation

factors, and **adenosine receptors**.

50. The method of claim 49, wherein said providing terminates postpartum.

51. A method of determining the effect of an environmental conditions on asthma which comprises comparing a mouse comprising a tissue-specific **ADA** transgene said mouse being homozygous for a null **Ada** allele and subjected to the environmental condition to a mouse comprising a tissue-specific **ADA** transgene said mouse being homozygous for a null **Ada** allele and not subjected to the environmental condition.

52. A composition comprising a placenta specific promoter.

=> s l10 not (l11 or l13)
L14 56 L10 NOT (L11 OR L13)

=> d l14,cbib,clm,40-56

L14 ANSWER 40 OF 56 USPATFULL on STN
1998:75453 Methods and kits for the detection of endotoxin.
Neely, Constance F., Philadelphia, PA, United States
Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 5773306 19980630
APPLICATION: US 1996-652928 19960524 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of determining endotoxin levels in a sample comprising: (a) binding an A_1 **adenosine receptor** agent to A_1 **adenosine receptors**; (b) contacting the bound agent and A_1 **adenosine receptors** with a sample so that any endotoxin in the sample displaces the bound agent by binding to the A_1 **adenosine receptors**; and (c) determining the amount of displaced agent.

2. The method of claim 1 wherein the A_1 **adenosine receptor** agent is an A_1 **adenosine receptor antagonist**.

3. The method of claim 1 wherein the A_1 **adenosine receptor** agent is an A_1 **adenosine receptor** agonist.

4. A method of diagnosing septicemia in an animal comprising: (a) binding an A_1 **adenosine receptor** agent to A_1 **adenosine receptors**; (b) contacting the bound agent and A_1 **adenosine receptors** with a sample from an animal suspected of having septicemia so that any endotoxin in the sample displaces the bound agent by binding to the A_1 **adenosine receptors**; and (c) measuring an amount of displaced agent; and (d) determining the level of endotoxin in the sample so that septicemia can be diagnosed.

5. A kit for detection of endotoxin in a sample comprising: (a) a source of A_1 **adenosine receptors**; (b) a detectably labeled A_1 **adenosine receptor** agent; and (c) endotoxin standards.

6. A method for determining endotoxin levels in a sample comprising: (a) coating a solid phase support with an A_1 **adenosine receptor** capable of immobilizing endotoxin; (b) contacting the solid phase support with a sample suspected of containing endotoxin; and (c) contacting the solid phase support with a means for detecting endotoxin immobilized to the solid phase support.

7. A kit for detection of endotoxin comprising: (a) a solid phase support coated with an A_1 **adenosine receptor** capable of immobilizing endotoxin to the solid phase support; (b) a means for detecting endotoxin immobilized to the solid phase support; and (c) endotoxin standards.

L14 ANSWER 41 OF 56 USPATFULL on STN
1998:33938 Prevention and treatment of ischemia-reperfusion and endotoxin-related injury using adenosine and purino receptor **antagonists**.

Neely, Constance F., Philadelphia, PA, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 5733916 19980331
WO 9526728 19951012
APPLICATION: US 1996-716192 19960930 (8)
WO 1995-US3702 19950324 19960930 PCT 371 date 19960930 PCT 102(e) date
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of preventing or treating ischemia-reperfusion organ injury in an animal comprising administering to an animal an effective amount of a P_{2X} purinoceptor **antagonist** at a selected time so that ischemia-reperfusion organ injury is prevented or treated.

2. A method of preventing or treating endotoxin-related lung injury in an animal comprising administering to an animal an effective amount of an A_1 **adenosine receptor antagonist** so that endotoxin-related lung injury is prevented or treated.

3. The method of claim 2 further comprising administering an effective amount of a P_{2X} purinoceptor **antagonist**.

4. A method of preventing or treating endotoxin-related lung injury in an animal comprising administering to an animal an effective amount of a P_{2X} purinoceptor **antagonist** so that endotoxin-related lung injury is prevented or treated.

5. A composition comprising a selective A_1 andenosine receptor **antagonist** and a P_{2X} purinoceptor **antagonist**.

6. A method of preventing or treating ischemia-reperfusion organ injury comprising perfusing an organ with an effective amount of a selective A_1 **adenosine receptor antagonist** at a selected time so that ischemia-reperfusion injury of the organ is prevented or treated.

7. A method of preventing or treating ischemia-reperfusion organ injury comprising perfusing an organ with an effective amount of a compound comprising a selective A_1 **adenosine receptor antagonist** and a P_{2X} purinoceptor **antagonist** at a selected time so that ischemia-reperfusion injury of the organ is prevented or treated.

8. A method of preventing or treating ischemia-reperfusion organ injury comprising perfusing an organ with an effective amount of a P_{2X} purinoceptor **antagonist** at a selected time so that ischemia-reperfusion injury of the organ is prevented or treated.

9. A method of inhibiting organ injury in high risk patients for ischemia-reperfusion injury comprising administering to a patient an effective amount of a compound comprising a selective A_1 **adenosine receptor antagonist** and a P_{2X} purinoceptor **antagonist** so that injury from ischemia-reperfusion is inhibited.

10. A method of inhibiting organ injury in high risk patients for ischemia-reperfusion injury comprising administering to a patient an effective amount of a P_{2X} purinoceptor **antagonist** so that injury from ischemia-reperfusion is inhibited.

L14 ANSWER 42 OF 56 USPATFULL on STN
97:59214 Inhibition of eosinophil activation through A3 **adenosine receptor** antagonism.
Jacobson, Marlene A., Elkins Park, PA, United States
Johnson, Robert G., Rosemont, PA, United States
Salvatore, Christopher A., North Wales, PA, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
US 5646156 19970708
APPLICATION: US 1994-233009 19940425 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for treating or preventing allergic and inflammatory diseases which comprises contacting the eosinophil A3 **adenosine receptor** with an amount of an A3 **adenosine receptor** subtype

specific **antagonist** effective to prevent eosinophil activation.

2. The method of claim 1 wherein said allergic and inflammatory diseases are selected from asthma, hypersensitivity, rhinitis, hay fever, serum sickness, allergic vasculitis, atopic dermatitis, dermatitis, psorasis, eczema, idiopathic pulmonary fibrosis, eosinophillic cholecystitis, chronic airway inflammation, hypereosinophilic syndromes, eosinophillic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, carcinomatosis, eosinophilic granuloma and familial histiocytosis.

3. The method of claim 2 wherein said **antagonist** is: ##STR4## wherein R_1, R_2, and R_3, independently, are as defined below:

R_1	R_2	R3
lower alkyl	benzyl	benzyl-acid
	halogenated benzyl	
	amino-benzyl	
	halogenated amino-benzyl.	

4. The method of claim 3 wherein said xanthine is: ##STR5## wherein R_1, R_2, and R_3, independently, are as defined below:

R_1	R_2	R3
$--C_3H_7$	$--C_3H_7$	$--CH_2--C_6H_4--O$-acid
$--CH_3$		
benzyl	$--CH_2--COO--$	
$--C_2H_5$		
halogenated indole	benzyl	
aminobenzyl halogenated	aminobenzyl	

wherein said acid is -indole, -carboxylate, sulphonate, phosphonate.

5. The method of claim 4 wherein the xanthine is selected from the group consisting of IABOPX, and BW-A1433.

6. A method for preventing or treating asthma, hypersensitivity, rhinitis, hay fever, serum sickness, allergic vasculitis, atopic dermatitis, dermatitis, psorasis, eczema, idiopathic pulmonary fibrosis, eosinophillic cholecystitis, chronic airway intimation, hypereosinophilic syndromes, eosinophillic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, carcinomatosis, eosinophilic granuloma and familial histiocytosis in a human which comprises administering an amount of a xanthine or a xanthine derivative having an affinity for the A3 subtype of the human **adenosine receptor** on eosinophils which is at least one order of magnitude greater than the affinity for either the A1, A2a or A2b subtypes of the human **adenosine receptor** effective to antagonize activation of the **adenosine receptor** of the A3 subtype.

L14 ANSWER 43 OF 56 USPATFULL on STN
96:103746 Methods for protecting tissues and organs from ischemic damage.
Downey, James M., Mobile, AL, United States
Mullane, Kevin M., Del Mar, CA, United States
Gensia, Inc., San Diego, CA, United States (U.S. corporation)South Alabama Medical Science Foundation, Mobile, AL, United States (U.S. corporation)
US 5573772 19961112
APPLICATION: US 1994-214942 19940317 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A method for reducing ischemic damage to an organ having A3 **adenosine receptors** for those patients at risk of ischemic damage, comprising the step of: administering to the organ a therapeutic amount of an agonist to the A3 **adenosine receptor**, wherein the A3 **adenosine receptor** agonist is administered orally.

2. A method as in claim 1 wherein the A3 **adenosine receptor** agonist is APNEA.

3. A method as in claim 1 wherein the organ having A3 **adenosine receptors** is the heart.

4. A method as in claim 1 further comprising the step of administering an **antagonist** to A1 **adenosine receptors**, wherein the A1 **adenosine receptor antagonist** is administered orally.

5. A method as in claim 4 wherein the A1 **adenosine receptor antagonist** is administered to the organ having A3 **adenosine receptors** before the A3 **adenosine receptor** agonist is administered.

6. A method as in claim 4 wherein the organ is the heart.

7. A method as in claim 4 wherein the **antagonist** to A1 **adenosine receptors** is selected from the group consisting of DPCPX, XAC, BW-A844U, N-0861, KF 15372 and KFM 19.

8. A method as in claim 1 wherein the A3 **adenosine receptor** agonist has a selectivity for the A3 **adenosine receptor** of at least about 10:1 over A1 and A2 **adenosine receptors**.

9. A method as in claim 1 wherein the A3 **adenosine receptor** agonist has a selectivity for the A3 **adenosine receptor** of at least about 100:1 over A1 and A2 **adenosine receptors**.

10. A method as in claim 1 wherein the A3 **adenosine receptor** agonist is administered prophylactically.

11. A method for preconditioning tissues and organs having A3 **adenosine receptors** to protect the tissues and organs from ischemic damage for patients in which preconditioning would be beneficial, comprising the step of: administering to the patient an ischemic damage reducing amount of an agonist to the A3 **adenosine receptor** using an administration technique selected from the group consisting of intravenous administration, oral administration and perfusion of the tissues and organs.

12. A method as in claim 11 wherein the agonist to the A3 **adenosine receptor** is selected from the group consisting of N^6 -(2-(4-aminophenyl)ethyl)adenosine (APNEA), N^6 -2-(4-amino-3-iodophenyl)ethyladenosine (I-APNEA), 5'-N-ethylcarboxamidoadenosine (NECA), N^6 -benzyladenosine-5'-N-methyluronamide, N^6 -(3-bromobenzyl)-adenosine-5'-N-methyluronamide, N^6 -(3-iodobenzyl)adenosine-5'-N-methyluronamide, and N^6 -(3-chlorobenzyl)adenosine-5'-N-methyluronamide.

13. A method as in claim 11 wherein the organ having A3 **adenosine receptors** is the heart.

14. A method as in claim 13 wherein the A3 **adenosine receptor** agonist is administered by perfusing the heart during surgery.

15. A method as in claim 13 wherein the A3 **adenosine receptor** agonist is intravenously administered before and during surgery.

16. A method as in claim 11 wherein the organ having A3 **adenosine receptors** is the brain.

17. A method as in claim 16 wherein the A3 **adenosine receptor** agonist is administered during surgery.

18. A method as in claim 11 wherein the A3 **adenosine receptor** agonist has a selectivity for the A3 **adenosine receptor** of at least about 10:1 over A1 **adenosine receptors**.

19. A method as in claim 18 wherein the selectivity is 100:1.

20. A method as in claim 11 wherein the A3 **adenosine receptor** agonist has a selectivity for the A3 **adenosine receptor** of at least about 10:1 over A2 **adenosine receptors**.

21. A method as in claim 20 wherein the selectivity is 100:1.

22. A method for preconditioning tissues and organs having A1 and A3 **adenosine receptors** to protect the organ from ischemic damage for patients in need of preconditioning, comprising the steps of: administering to the patient an **antagonist** to the A1 **adenosine receptor**, wherein the amount of A1 **adenosine receptor antagonist** administered to the patient is sufficient to prevent stimulation of the A1 **adenosine receptors** that is adverse to the patient; and administering to the patient an ischemic damage reducing amount of an agonist to the A3 **adenosine receptor**, wherein the A1 **adenosine receptor antagonist** and the A3 **adenosine receptor** agonist are administered orally, intravenously or by perfusion of the tissues and organs.

23. A method as in claim 22 wherein the A1 **adenosine receptor antagonist** and the A3 **adenosine receptor** agonist are administered to protect the heart from ischemic damage.

24. A method as in claim 22 wherein the A1 **adenosine receptor antagonist** and the A3 **adenosine receptor** agonist are administered to protect the brain from ischemic damage.

25. A method as in claim 22 wherein the A3 **adenosine receptor** agonist is selected from the group consisting of N^6 -(2-(4-aminophenyl)ethyl)adenosine (APNEA), N^6 -2-(4-amino-3-iodophenyl)ethyladenosine (I-APNEA), 5'-N-ethylcarboxamidoadenosine (NECA), N^6 -benzyladenosine-5'-N-methyluronamide, N^6 -(3-bromobenzyl)adenosine-5'-N-methyluronamide, N^6 -(3-iodobenzyl)adenosine-5'-N-methyluronamide, and N^6 -(3-chlorobenzyl)adenosine-5'-N-methyluronamide.

26. A method as in claim 22 wherein the A1 **adenosine receptor antagonist** is selected from the group consisting of DPCPX, XAC, BW-A844U, N-0861, KF 15372 and KFM 19.

27. A method as in claim 22 further comprising the step of administering to tissues and organs having A2 **adenosine receptors** an **antagonist** to the A2 **adenosine receptor**, wherein the A2 **adenosine receptor antagonist** is administered orally, intravenously or by perfusion of the tissues and organs.

28. A method as in claim 27 wherein the A2 **adenosine receptor antagonist** is selected from the group consisting of DATSX and DM TSX.

29. A method for protecting an organ having A3 **adenosine receptors** for patients in need thereof, comprising the step of: administering an A3 **adenosine receptor** agonist to the patient using an administration technique selected from the group consisting of oral, intravenous and perfusion.

30. A method as in claim 29 wherein the organ having A3 **adenosine receptors** is the heart.

31. A method as in claim 30 wherein the A3 **adenosine receptor** agonist is administered during surgery.

32. A method as in claim 31 wherein the A3 **adenosine receptor** agonist has a selectivity of 10:1 over A1 and A2 **adenosine receptors**.

33. A method as in claim 29 wherein the organ having A3 **adenosine receptors** is the brain.

34. A method as in claim 29 further comprising the step of administering to tissues and organs having A2 **adenosine receptors** an **antagonist** to the A2 **adenosine receptor**, wherein the A2 **adenosine receptor antagonist** is administered orally, intravenously or by perfusion of the tissues and organs.

35. A method as in claim 34 wherein the A2 **adenosine receptor antagonist** is selected from the group consisting of DATSX and DM TSX.

L14 ANSWER 44 OF 56 USPATFULL on STN
96:49931 Non-invasive method of determining inflammation of the gastrointestinal tract.
Wilson, Richard A., Lake Oswego, OR, United States
Oregon Health Sciences University, Portland, OR, United States (U.S. corporation)
US 5524622 19960611
APPLICATION: US 1994-309255 19940920 (8)
DOCUMENT TYPE: Utility; Granted.
CLM What is claimed is:
1. A method of determining the presence of inflammation in a region of a gastrointestinal tract of a subject, comprising the steps of: introducing an arterial dilating agent into the subject in a sufficient amount to dilate arteries to the region; introducing a blood flow marking medium into the subject in a sufficient amount that the blood flow marking medium collects in an inflamed region of the gastrointestinal tract; and monitoring an amount of blood flow marking medium appearing in the region, thereby providing an indication of the presence or absence of inflammation in the region of the gastrointestinal tract.

2. The method of claim 1 in which the arterial dilating agent is selected from the group of arterial dilating agents consisting of dipyridamole, adenosine and other **adenosine receptor** agonists, nitroglycerin compounds, hydralazine, calcium channel **antagonists**, and angiotensin converting enzyme inhibitors.

3. The method of claim 1 in which the blood flow marking medium is selected from the group consisting of radiolabelled blood flow tracers selected from the group consisting of thallium-201, technetium-99m labelled sestamibi and teboroxime, rubidium-81 and rubidium-82, potassium-43, oxygen-15 labelled water, and copper-67.

4. The method of claim 3 in which the monitoring step comprises quantitating an amount of blood flow marking medium present in the region of the gastrointestinal tract and liver of the subject by: measuring the radioactive emissions produced by the blood flow marking medium in the region of the gastrointestinal tract and liver; and determining whether the measured emissions in the region of the gastrointestinal tract are less than, equal to, or greater than the measured emissions in the liver.

5. The method of claim 1 in which the region of the gastrointestinal tract is that of a human being.

6. A method of detecting esophagitis or gastritis in a subject, comprising the steps of: injecting an intravenous dose of dipyridamole into a subject in a sufficient amount to dilate an arterial supply of the esophagus and stomach of the subject; injecting an intravenous dose of thallium-201 into the subject in a sufficient amount to allow uptake of the thallium-201 into an inflamed esophageal or gastric mucosa; monitoring emissions of gamma radiation with a gamma camera that images the esophagus, stomach and liver; and comparing an intensity of gamma emissions from the liver, esophagus and stomach to determine whether the gamma emissions of the esophagus or stomach are greater or less than gamma emissions from the liver.

7. The method of claim 6 wherein the dipyridamole is injected in a dose of at least 0.56 mg/kg, and the thallium-201 is injected intravenously in a dose of 3 mCi.

8. The method of claim 7 wherein the step of monitoring emissions comprises obtaining photographic images with the gamma camera, wherein areas of increased blood flow are darker than areas having less blood flow.

9. The method of claim 8 wherein the step of obtaining photographic images with the gamma camera comprises obtaining photographic images beginning 3 minutes after thallium-201 injection.

10. A method of detecting inflammation in a gastrointestinal tract of a

human subject, comprising the steps of: injecting an intravenous dose of at least 0.56 mg/kg of dipyridamole into the subject; injecting an intravenous dose of 3.0 mCi thallium-201 into the subject; beginning at least three minutes after injection of the thallium-201, monitoring emissions of gamma radiation with a gamma camera to provide images of the gastrointestinal tract and liver of the subject; and comparing an intensity of gamma emissions from the gastrointestinal tract to the liver to determine whether the gamma emissions from the gastrointestinal tract are greater or less than gamma emissions from the liver.

L14 ANSWER 45 OF 56 USPATFULL on STN
96:27200 Compositions and methods for the prevention and treatment of ischemia-reperfusion organ injury.
Neely, Constance F., Philadelphia, PA, United States
Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 5504090 19960402
APPLICATION: US 1994-219946 19940330 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of preventing ischemia-reperfusion organ injury comprising administering to an animal an effective amount of a selective A_1 **adenosine receptor antagonist** at a selected time prior to a surgical procedure in which ischemia is expected to occur so that organ injury resulting from the surgical procedure is prevented.

2. The method of claim 1 wherein the animal is a human.

3. The method of claim 1 wherein the organ injury is in lung tissue.

4. The method of claim 1 wherein the surgical procedure comprises organ transplantation.

5. A method of inhibiting organ injury in high risk patients for ischemia-reperfusion injury comprising administering to a patient an effective amount of a selective A_1 **adenosine receptor antagonist** so that injury from ischemiareperfusion is inhibited.

6. The method of claim 5 wherein the ischemiareperfusion injury is resulting from a bowel ischemia and reperfusion, sepsis, anaphylaxis, hemorrhagic shock, or trauma.

7. The method of claim 1 wherein the selective A_1 **adenosine receptor antagonist** of the composition comprises an alkyl xanthine derivative.

8. The method of claim 1 wherein the selective A_1 **adenosine receptor antagonist** of the composition comprises a 7-deaza-2-phenyladenine compound.

9. The method of claim 1 wherein the selective Am **adenosine receptor antagonist** of the compositions is DPCPX, XAC, XCC, 8-(noradamantan-3-yl)-1,3-dipropylxanthine, 8-cyclopropyl-methyl)-1,3-dipropyl xanthine, 1-propyl-3-(4-amino-3-iodophenylethyl)-8-cyclopentylxanthine, DPSPX, 7,8-dihydro-8-ethyl-2-(3-noradamantyl)-4-propyl-1H-imidazo[2,1-i]purin-5(4H)-one, (R)-7,8-dimethyl-2-phenyl-9-(1-phenylethyl)-7-deazaadenine or (±)-N^6 -endonorbornan-2-yl-9-methyladenine.

10. The method of claim 1 wherein the selective A_1 **adenosine receptor antagonist** is XAC.

11. The method of claim 1 wherein the selective A_1 **adenosine receptor antagonist** is DPCPX.

L14 ANSWER 46 OF 56 USPATFULL on STN
95:75747 Methods for protecting tissues and organs from ischemic damage.
Downey, James M., Mobile, AL, United States
Mullane, Kevin, Del Mar, CA, United States
Gensia, Inc., San Diego, CA, United States (U.S. corporation)South Alabama Medical Science Foundation, Mobile, AL, United States (U.S. corporation)
US 5443836 19950822

APPLICATION: US 1993-33310 19930315 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for reducing ischemic damage to an organ having A3 **adenosine receptors** for those patients at risk of ischemic damage, comprising the step of: administering an ischemic damage reducing amount of an agonist to the A3 **adenosine receptor** using an administration technique selected from the group consisting of intravenous administration and perfusion of the organ.

2. A method as in claim 1 wherein the agonist to the A3 **adenosine receptor** is APNEA.

3. A method as in claim 1 wherein the organ having A3 **adenosine receptors** is the heart.

4. A method as in claim 1 further comprising the step of administering an **antagonist** to A1 **adenosine receptors** using an administration technique selected from the group consisting of intravenous administration and perfusion of the organ.

5. A method as in claim 4 wherein the **antagonist** to A1 **adenosine receptor** is administered to the organ having A3 **adenosine receptors** before the agonist to the A3 **adenosine receptor** is administered.

6. A method as in claim 4 wherein the organ is the heart.

7. A method as in claim 4 wherein the **antagonist** to A1 **adenosine receptors** is selected from the group consisting of DPCPX, XAC, BW-A844u, BW-A844U, N-0861, KF 15372 and KFM 19.

8. A method for preconditioning an organ having A1 and A3 **adenosine receptors** to protect the organ from ischemic damage for patients in need of preconditioning, comprising the steps of: administering to the patient an **antagonist** to the A1 **adenosine receptor**, wherein the amount of A1 **adenosine receptor antagonist** administered to the patient is sufficient to prevent stimulation of the A1 **adenosine receptor**; and administering to the patient an ischemic damage reducing amount of an agonist to the A1 and A3 **adenosine receptors**, wherein both the **antagonist** to the A1 **adenosine receptor** and the agonist to the A1 and A3 **adenosine receptors** are administered intravenously or by perfusion of the organ.

9. A method as in claim 8 wherein the **antagonist** to the A1 **adenosine receptor** is selected from the group consisting of DPCPX, XAC, BW-A844u, BW-A844U, N-0861, KF 15372 and KFM 19.

10. A method as in claim 8 wherein the **antagonist** to the A1 **adenosine receptor** is administered to the patient before the agonist to the A1 and A3 **adenosine receptors** is administered.

11. A method as in claim 8 wherein the agonist to the A1 and A3 **adenosine receptors** is selected from the group consisting of NECA and adenosine.

12. A method as in claim 8 wherein the organ is the heart.

13. A method for preconditioning tissues and organs having A3 **adenosine receptors** to protect the tissues and organs from ischemic damage for patients in which preconditioning would be beneficial, comprising the step of: administering to the patient an ischemic damage reducing amount of an agonist to the A3 **adenosine receptor**, wherein the A3 **adenosine receptor** agonist is administered intravenously or by perfusion.

14. A method as in claim 13 wherein the organ having A3 **adenosine receptors** is the heart.

15. A method as in claim 13 wherein the agonist to the A3 **adenosine receptor** is APNEA.

94:42348 Substituted carbamoyl and oxycarbonyl derivatives of biphenylmethylamines.

Ashton, Wallace T., Clark, NJ, United States
Chang, Linda L., Wayne, NJ, United States
Greenlee, William J., Teaneck, NJ, United States
Hutchins, Steven M., Iselin, NJ, United States
Rivero, Ralph A., Tinton Falls, NJ, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

US 5312820 19940517
APPLICATION: US 1992-917642 19920717 (7)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A compound of structural formula: ##STR33## or a pharmaceutically acceptable salt thereof wherein: A, B, C, and D are independently --CH.dbd. or --N.dbd., with the proviso that at least two of them are --CH.dbd.; X is --O-- or --N(R^7)--; R^1 is (a) --CO_2 R^4, (b) --SO_3 R^5, (c) --$NHSO_2$ CF_3, (d) --$PO(OR^5)_2$, (e) --SO_2 --NH--R^9, (f) --$CONHOR^5$, (g) --SO_2 NH-heteroaryl, (h) --CH_2 SO_2 NH-heteroaryl, (i) --SO_2 $NHCOR^{23}$, (j) --CH_2 SO_2 $NHCOR^{23}$, (k) --$CONHSO_2$ R^{23}, (l) --CH_2 $CONHSO_2$ R^{23}, (m) --$NHSO_2$ $NHCOR^{23}$, (n) --$NHCONHSO_2$ R^{23}, (o) --SO_2 $NHSO_2$ R^{23}, (p) --SO_2 $NHCO_2$ R^{20}, (q) --SO_2 $NHCONHR^{20}$, ##STR34## wherein: Y is (1) --CO_2 R^4, (2) --SO_3 R^5, (3) --$NHSO_2$ CF_3, (4) --$PO(OR^5)_2$, or (5) --SO_2 --NH--R^9 ; (6) 1H-tetrazol-5-yl; R^{2a} and R^{2b} are each independently: (a) hydrogen, (b) halo, (c) --NO_2, (d) --NH_2, (e) C_1 -C_4 -alkylamino, (f) --SO_2 NHR^9, (g) --CF_3, (h) C_1 -C_4 -alkyl (i) C_1 -C_4 -alkoxy; R^{3a} is (a) --H, (b) halo, (c) C_1 -C_6 -alkyl, (d) C_1 -C_6 -alkoxy, (e) C_1 -C_6 -alkoxy-C_1 -C_4 -alkyl; R^{3b} is (a) --H, (b) --halo, (c) --NO_2, (d) C_1 -C_6 -alkyl, (e) C_1 -C_5 -alkylcarbonyloxy, (f) C_3 -C_6 -cycloalkyl (g) C_1 -C_6 -alkoxy, (h) --$NHSO_2$ R^4, (i) hydroxy-C_1 -C_4 -alkyl, (j) aryl-C_1 -C_4 -alkyl (k) C_1 -C_4 -alkylthio (l) C_1 -C_4 -alkylsulfinyl (m) C_1 -C_4 -alkylsulfonyl (n) --NH_2 (o) C_1 -C_4 -alkylamino (p) di(C_1 -C_4 -alkyl)amino (q) --CF_3 (r) --SO_2 --NHR^9 (s) aryl; (t) furyl; R^4 is H, C_1 -C_6 -alkyl, --CH_2 -aryl or aryl; R^5 is H or --CH(R^4)--O--CO--R^{4a} wherein R^{4a} is C_1 -C_6 -alkyl, aryl or --CH_2 -aryl; R^6 is (a) C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl or C_2 -C_6 -alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C_3 -C_7 -cycloalkyl, halo, C_1 -C_4 -alkoxy, --NH_2, --NH(C_1 -C_4 -alkyl), --N(C_1 -C_4 -alkyl)$_2$, --NH--SO_2 R^4, --$COOR^4$, --SO_2 NHR^9, and C_1 -C_4 -alkylthio, (b) C_3 -C_7 -cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy, C_1 -C_4 -alkylthio, OH, perfluoro-C_1 -C_4 -alkyl, and halo, (c) C_3 -C_7 -cycloalkyl-C_1 -C_3 -alkyl wherein the cycloalkyl is unsubstituted or substituted as in (b) above, (d) aryl, or (e) heteroaryl; R^7 is (a) H, (b) phenyl unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of halo, C_1 -C_4 -alkoxy, C_1 -C_4 -alkyl, --NO_2, --CF_3, --SO_2 NR^9 R^{10}, C_1 -C_4 -alkylthio, --OH, --NH_2, --$COOR^4$, C_3 -C_7 -cycloalkyl, and C_3 -C_{10} -alkenyl, (c) C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl or C_2 -C_6 -alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, heteroaryl, C_3 -C_7 -cycloalkyl, halo, C_1 -C_4 -alkoxy, --NH_2, --NH(C_1 -C_4 -alkyl), --N(C_1 -C_4 -alkyl)$_2$, --NH--SO_2 R^4, --$COOR^4$, --SO_2 NHR^9, and C_1 -C_4 -alkylthio, (d) heteroaryl, or (e) C_3 -C_7 -cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy, C_1 -C_4 -alkylthio, --OH, --$COOR^4$, perfluoro-C_1 -C_4 -alkyl, and halo; R^8 is --H, halo, --CF_3, --CH_3,

--OCH_3 or --NO_2 ; R^7 and R^8 when joined together
form a ring with the atoms to which they are attached such that R^7
-R^8 is (a) --Y--$(CH_2)_n$ --Z, wherein n is 1 or 2; Y is a
single bond, --C(O)-- or --C(R^{14})(R^{15})--; Z is a single bond,
--O--, --S(O)$_p$ --, --N(R^{16})--, --C(O)--, --CF_2 -- or
--C(R^{14})(R^{15})--; and p is 0, 1 or 2 (b) ##STR35## with the
proviso that: (1) Q is a single bond or --CO--; (2) T is a single bond
or --CO--; and (3) at least one of Q and T is a single bond, (c)
##STR36## (d) ##STR37## ##STR38## wherein U is --O--, --S--, --C(O)--,
--CF_2 -- or --CH_2 --, or ##STR39## R^9 is H, C_1
-C_5 -alkyl, aryl or --CH_2 -aryl; R^{10} is H, C_1
-C_4 -alkyl, or R^9 and R^{10} when together form
--$(CH_2)_m$ -- where m is 3-6; R^{11} is H, C_1 -C_6
-alkyl, C_2 -C_4 -alkenyl, C_1 -C_4 -alkoxy-C_1
-C_4 -alkyl, or --CH_2 --C_6 H_4 R^{21} ; R^{12} is
--CN, --NO_2 or --CO_2 R^4 ; R^{13} is H, C_2 -C_4
-alkanoyl, C_1 -C_6 -alkyl, allyl, C_3 -C_6 -cycloalkyl,
phenyl or benzyl; R^{14} and R^{15} are independently H, C_1
-C_4 -alkyl, aryl, aryl-C_1 -C_2 -alkyl, C_1 -C_4
-alkoxycarbonyl, --CO_2 H or --CH_2 OH; R^{16} is (a) C_1
-C_6 -alkyl, either unsubstituted or substituted with C_1
-C_4 -alkoxy, C_1 -C_4 -alkyl-S(O)$_p$ --, --CF_3,
--OH, --CN, C_1 -C_4 -alkoxycarbonyl, --CO_2 H, --CONR^9
R^{10} or --CO-aryl, (b) C_3 -C_6 -alkenyl, (c) C_3
-C_6 -cycloalkyl, (d) aryl, (e) heteroaryl, (f) --COR^{20}, (g)
--CO_2 R^{20}, (h) --CONR^9 R^{10}, or (i) --SO_2
R^{20} ; R^{17} and R^{18} are independently H, C_1 -C_4
-alkyl, aryl, aryl-C_1 -C_2 -alkyl, C_1 -C_4 -alkoxy,
--CF_3, halo, C_1 -C_4 -alkoxycarbonyl, --CO_2 H or
--CH_2 OH; R^{19} is C_1 -C_4 -alkyl, C_1 -C_4
-alkoxy, halo, --CF_3, C_1 -C_4 -alkyl-S(O)$_p$ --,
CF_3 SO_2 --, --CN, --NO_2, C_1 -C_4
-alkoxycarbonyl, --CO_2 H, or --CH_2 OH; R^{20} is C_1
-C_6 -alkyl, aryl or aryl-C_1 -C_2 -alkyl; R^{21} is H,
--NO_2, --NH_2, --OH or --OCH_3 ; R^{23} is (a) phenyl,
unsubstituted or substituted with one or two substituents selected from
halo, --CH_3 and --CF_3, at least one or which occupies an
ortho-position; (b) heteroaryl, selected from the group consisting of
furan-2-yl, thiophen-2-yl, benzo[b]furan-2-yl, benzo[b]thiophene-2-yl,
furan-3-yl, thiophen-3-yl, and oxazol-5-yl, unsubstituted or substituted
with one or two substituents selected from halo, --CH_3 and CF_3
wherein at least one of the substituents is located adjacent to the
carbonyl substituent or to a ring heteroatom or both; (c) C_3
-C_6 -alkyl; (d) C_3 -C_7 -cycloalkyl, unsubstituted or
substituted at the 1- or 2-position or both with one to three
substituents selected from halo, --CH_3 and --CH_2 CH_3 ;
(e) C_7 -C_8 -bi- or tricycloalkyl; (f) saturated 5- or
6-membered heterocyclyl linked through a carbon atom and containing one
or two heteroatoms selected from oxygen and sulfur selected from the
group consisting of tetrahydrofuroyl, 1,3-dithiolane, and 1,3-dithiane.
R^{24} is H, or R^{25}, R^{25} is (a) phenyl unsubstituted or
substituted with 1 or 2 substituents selected from the group consisting
of halo, --O--C_1 -C_4 -alkyl, C_1 -C_4 -alkyl,
--NO_2, --CF_3, --SO_2 NR^9 R^{10}, --S--C_1
-C_4 -alkyl, --OH, --NH_2, --$COOR^4$, C_3 -C_7
-cycloalkyl, and C_3 -C_{10} -alkenyl, (b) C_1 -C_6
-alkyl, C_2 -C_6 -alkenyl or C_2 -C_6 -alkynyl each of
which is unsubstituted or substituted with one or more substituents
selected from the group consisting of aryl, C_3 -C_7
-cycloalkyl, halo, --OH, --O--C_1 -C_4 -alkyl, --NH_2,
--NH(C_1 -C_4 -alkyl), --N(C_1 -C_4 -alkyl)$_2$,
--NH--SO_2 R^4, --$COOR^4$, --SO_2 NHR^9, and
--S--C_1 -C_4 -alkyl, (c) an unsubstituted, monosubstituted or
disubstituted aromatic 5 or 6 membered ring comprising one or two
heteroatoms selected from the group consisting of N, O, and S, and
wherein the substituents are members selected from the group consisting
of --OH, --SH, C_1 -C_4 -alkyl, C_1 -C_4 -alkyloxy,
--CF_3, --$COOR^4$, halo, and NO_2, or (d) C_3 -C_7
-cycloalkyl unsubstituted or substituted with one or more substituents
selected from the group consisting of C_1 -C_4 -alkyl,
--O--C_1 -C_4 -alkyl, --S--C_1 -C_4 -alkyl, --OH,
--$COOR^4$, perfluoro--C_1 -C_4 -alkyl, halo; V is (a) H, (b)

C_1 -C_5 -alkoxy, (c) C_1 -C_5 -alkyl, (d) hydroxy, (e) C_1 -C_5 -alkyl-$S(O)_p$, (f) --CN, (g) --NO_2, (h) --NR^9 R^{10} ; (i) C_1 -C_5 -alkyl-$CONR^9$ R^{10}, (j) --$CONR^9$ R^{10} (k) --CO_2 R^9, (l) C_1 -C_5 -alkyl-carbonyl, (m) CF_3, (n) halogen, (o) hydroxy-C_1 -C_4 -alkyl-, (p) carboxy-C_1 -C_4 -alkyl-, (q) --1H-tetrazol-5-yl, (r) --NH--SO_2 CF_3, (s) aryl, (t) C_1 -C_5 -alkyl-CO_2 R^9, (u) aryloxy, (v) aryl-C_1 -C_3 -alkoxy, (w) aryl-C_1 -C_3 -alkyl, (x) carboxyphenyl, (y) heteroaryl, (z) 2-oxazolin-2-yl unsubstituted or bearing one or more C_1 -C_4 -alkyl substituents, (aa) --$(CH_2)_t$ $OCOR^{25}$, (bb) --$(CH_2)_t$ $OCONR^{24}$ R^{25}, (cc) --$(CH_2)_t$ NR^{24} COR^{25}, (dd) --$(CH_2)_t$ NR^{24} CO_2 R^{25}, (ee) --$(CH_2)_t$ NR^{24} $CONR^{24}$ R^{25}, (ff) --$(CH_2)_t$ NR^{24} $CON(CH_2$ $CH_2)_2$ L, (gg) --$(CH_2)_t$ $OCON(CH_2$ $CH_2)_2$ L, (hh) --$N(CH_2$ $CH_2)_2$ L, (ii) --C_1 -C_5 -alkyl-$CON(CH_2$ $CH_2)_2$ L, or (jj) --$CON(CH_2$ $CH_2)$L; t is 0, 1 or 2; and L is a bond, --CH_2 --, --O--, --$S(O)_p$ -- or --NR^9 --, wherein heteroaryl is selected from the group consisting of pyridine, pyrimidine, pyrazine, triazine, furan, thiophene, oxazole, thiazole, imidazole, triazole and thiadiazole, which is unsubstituted or fused to a benzo group and wherein the mono- or bicyclic system can be unsubstituted or substituted with one or two substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, --CF_3, halo, --NO_2, --CN, --OH, --NH_2, --$NH(C_{1-4}$ alkyl), --$N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxycarbonyl and --CO_2 H.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein X is --$N(R^7)$-- wherein R^7 and R^8 are joined to form a ring such that R^7 -R^8 is --Y--$(CH_2)_n$ --Z--.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof wherein Y is a single bond, $C(R^{14})(R^{15})$ or CO; Z is a single bond; n=1 or 2; and A, B, C and D are each --CH.dbd.; R^1 is --SO_2 $NHCOR^{23}$, --SO_2 $NHCO_2$ R^{20}, --SO_2 $NHCONHR^{20}$ or 1H-tetrazol-5-yl; R^{2a}, R^{2b}, R^{3a} and R^{3b} are independently H, C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy or halo; R^6 is C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, C_3 -C_7 -cycloalkyl, or C_3 -C_7 -cycloalkyl-C_1 -C_3 -alkyl; and V is H, C_1 -C_5 -alkyl, C_1 -C_5 -alkoxy, --CF_3, halo, --NO_2, --NR^9 R^{10}, --NR^{24} COR^{25}, --NR^{24} CO_2 R^{25}, --NR^{24} $CONR^{24}$ R^{25}, --NR^{24} $CON(CH_2$ $CH_2)_2$ L, --$CONR^9$ R^{10}, --$CON(CH_2$ $CH_2)_2$ L, or --$CO(C_1$ -C_5 -alkyl);

4. The compound of claim 3 or a pharmaceutically acceptable salt thereof which is: 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]indoline; 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-1,2,3,4-tetrahydroquinoline; 1-[N-butyl-N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]carbamoyl]-1,2,3,4-tetrahydroquinoline; 1-[N-butyl-N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]carbamoyl]-3,4-dihydro-2(1H)quinolinone. 1-[N-[[2'-[N-(t-butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-N-butylcarbamoyl]-1,2,3,4-tetrahydroquinoline; 1-[N-pentyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]carbamoyl]-1,2,3,4-tetrahydroquinoline; ethyl 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-1,2,3,4-tetrahydroquinoline-2-carboxylate; 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-7-nitro-1,2,3,4-tetrahydroquinoline; 7-amino-1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-1,2,3,4-tetrahydroquinoline; or 7-(butyrylamino)-1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-1,2,3,4-tetrahydroquinoline.

5. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein X is --$N(R^7)$-- and R^7 and R^8 are joined to form a ring such that R^7 --R^8 is --Y--$(CH_2)_n$ --Z wherein Y is a single bond; Z is O, $N(R^{16})$, S, --CF_2 --,

--C(R^{14})(R^{15})-- or --C(O)--; n is 2; A, B, C and D are each --CH.dbd. R^1 is --SO_2 $NHCOR^{23}$, --SO_2 $NHCO_2$ R^{20}, --SO_2 $NHCONHR^{20}$ or 1H-tetrazol-5-yl; R^{2a}, R^{2b}, R^{3a} and R^{3b} are independently H, C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy or halo; R^6 is C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, C_3 -C_7 -cycloalkyl, or C_3 -C_7 -cycloalkyl-C_1 -C_3 -alkyl; and V is H, C_1 -C_5 -alkyl, C_1 -C_5 -alkoxy, --CF_3, or halo.

6. The compound of claim 5 or a pharmaceutically acceptable salt thereof which is: 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-3,4-dihydro-4(1H)quinolinone; 4-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-3,4-dihydro-2H-1,4-benzothiazine; 4-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-3,4-dihydro-2H-1,4-benzoxazine; 1-acetyl-4-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-1,2,3,4-tetrahydroquinoxaline; 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-4,4-difluoro-1,2,3,4-tetrahydroquinoline; or 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-4-methyl-1,2,3,4-tetrahydroquinoline.

7. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein R^7 and R^8 joined together are ##STR40## A, B, C and D are each --CH.dbd. or --N.dbd., R^1 is --SO_2 $NHCOR^{23}$, --SO_2 $NHCO_2$ R^{20}, --SO_2 $NHCONHR^{20}$ or 1H-tetrazol-5-yl; R^{2a}, R^{2b}, R^{3a} and R^{3b} are independently H, C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy or halo; R^6 is C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, C_3 -C_7 -cycloalkyl, or C_3 -C_7 -cycloalkyl-C_1 -C_3 -alkyl; and V is H, C_1 -C_5 -alkyl, C_1 -C_5 -alkoxy, --CF_3, or halo.

8. The compound of claim 7 or a pharmaceutically acceptable salt thereof which is: 10-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]acridan; 10-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-9(10H)-acridone; 10-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]phenoxazine; 3-chloro-1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]indazole; 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-3-methylindole; or 1-[N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamoyl]-2-methylbenzimidazole.

9. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein X is --N(R^7)-- wherein R^7 is aryl, heteroaryl, aryl-C_1 -C_6 -alkyl, or C_1 -C_6 -alkyl.

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof wherein A, B, C and D are each --CH.dbd. or --N.dbd.; R^1 is --SO_2 $NHCOR^{23}$, --SO_2 $NHCO_2$ R^{20}, --SO_2 $NHCONHR^{20}$ or -1H-tetrazol-5-yl; R^{2a}, R^{2b}, R^{3a}, R^{3b} are independently H, C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy, or halo; R^6 is C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, C_3 -C_7 -cycloalkyl; or C_3 -C_7 -cycloalkyl-C_1 -C_3 -alkyl; and R^{7-8} is H, halo, or --CF_3 V is H, C_1 -C_5 -alkyl, C_1 -C_5 -alkoxy, CF_3, halo, --NO_2, --NR^9 R^{10}, --NR^{24} COR^{25}, --NR^{24} CO_2 R^{25}, --NR^{24} $CONR^{24}$ R^{25}, --NR^{24} $CON(CH_2$ $CH_2)_2$ L, --$CONR^9$ R^{10}, --$CON(CH_2$ $CH_2)_2$ L, or --$CO(C_1$ -C_5 -alkyl);

11. The compound of claim 10 or a pharmaceutically acceptable salt thereof which is: 1-butyl-1-[[2'-N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-phenyl-3-(2-pyridyl)urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-1-pentyl-3-phenyl-3-(2-pyridyl)urea; 1-benzyl-3-butyl-3-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-1-phenylurea; 1-benzyl-3-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-pentyl-1-phenylurea; 1-butyl-1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphen

yl-4-yl]methyl]-3-methyl-3-[2-(trifluoromethyl)phenyl]urea; 1-methyl-3-pentyl-3-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1-[2-(trifluoromethyl)phenyl]urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-methyl-1-pentyl-3-[2-(trifluoromethyl)phenyl]urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-methyl-1-pentyl-3-phenylurea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-1-pentyl-3,3-diphenylurea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-(3-chloro-2-pyridyl)-1-pentyl-3-phenylurea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-(2-chlorophenyl)-1-pentyl-3-(2-pyridyl)urea; 1-benzyl-3-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-pentyl-1-[2-(trifluoromethyl)phenyl]urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-[2-chloro-5-(valerylamino)phenyl]-3-methyl-1-pentylurea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-(2-chlorophenyl)-3-methyl-1-pentylurea; 1-butyl-1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]-5'-propylbiphenyl-4-yl]methyl]-3-methyl-3-[2-(trifluoromethyl)phenyl]urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]-5'-ethylbiphenyl-4-yl]methyl]-3-[2-chloro-5-(propionylamino)phenyl]-3-methyl-1-pentylurea; 1-[[2'-[N-(t-butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-1-butyl-3-[2-chloro-5-(valerylamino)phenyl]-3-methylurea; 1-[[2'-[N-(n-butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-3-[2-chloro-5-(valerylamino)phenyl]-3-methyl-1-pentylurea; 1-[[2'-[N-(N-butylcarbamoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-[2-chloro-5-(valerylamino)phenyl]-3-methyl-1-pentylurea; 1-[5-(N-butylcarbamoyl)-2-chlorophenyl]-3-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-1-methyl-3-pentylurea; or 1-[[2'-[N-(3-chloro-2-furoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-methyl-1-pentyl-3-[2-(trifluoromethyl)phenyl]urea.

12. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein X is --O--.

13. The compound of claim 12 or a pharmaceutically acceptable salt thereof wherein R^1 is $--SO_2$ $NHCOR^{23}$, $--SO_2$ $NHCO_2$ R^{20}, $--SO_2$ $NHCONHR^{20}$ or -1H-tetrazol-5-yl; R^{2a}, R^{2b}, R^{3a}, R^{3b} are independently H, C_1 -C_4 -alkyl, C_1 -C_4 -alkoxy, or halo; R^6 is C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, C_3 -C_7 -cycloalkyl; or C_3 -C_7 -cycloalkyl C_1 -C_3 -alkyl; and

14. The compound of claim 13 or a pharmaceutically acceptable salt thereof which is: 2-(trifluoromethyl)phenyl N-butyl-N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]carbamate; or 2-(trifluoromethyl)phenyl N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-pentylcarbamate.

15. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein R^6 is heteroaryl and X is --O-- or NR^7.

16. The compound of claim 15 or a pharmaceutically acceptable salt thereof wherein R^6 is pyridyl or pyrimidyl.

17. The compound of claim 16 or a pharmaceutically acceptable salt thereof which is: 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-methyl-1-(2-methyl-4-pyridyl)-3-[2-(trifluoromethyl)phenyl]urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-3-methyl-1-(2,6-dimethyl-4-pyrimidyl)-3-[2-(trifluoromethyl)phenyl]urea; 1-(2-ethyl-4-pyridyl)-3-methyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-3-[2-(trifluoromethyl)phenyl]urea; 1-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]-5'-ethylbiphenyl-4-yl]methyl]-3-[2-chloro-5-(propionylamino)phenyl]-3-methyl-1-(2-methyl-4-pyridyl)urea; or 2-(trifluoromethyl)phenyl N-[[2'-[N-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-N-(2-methyl-4-pyridyl)carbamate.

18. A pharmaceutical composition useful in the treatment of hypertension which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 1.

19. The composition of claim 6 which includes another antihypertensive selected from a diuretic selected from hydrochlorothiazide, chlorothiazide, chlorthalidone, methyclothiazide, furosemide, ethacrynic acid, triamterene, amiloride and spironolactone; a calcium channel blocker, selected from diltiazem, felodipine, nifedipine, nitrendipine and verapamil; a β-adrenergic **antagonist** selected from timolol,

atenolol, metoprolol, propanolol, nadolol and pindolol; an angiotensin converting enzyme inhibitor selected from enalapril, lisinopril, captopril, ramipril, quinapril and zofenopril; a renin inhibitor selected from A-69729 and FK 744; an α-adrenergic **antagonist** selected from prazosin, doxazosin, and terazosin; a sympatholytic agent selected from methyldopa, clonidine and guanabenz; the antriopeptidase inhibitor, UK-79300; the serotonin **antagonist**, ketanserin; the A_2 **-adenosine receptor** agonist CGS 22492C; a potassium channel agonist selected from pinacidil and cromakalim; or another antihypertensive drug selected from reserpine, minoxidil, guanethidine, hydralazine hydrochloride and sodium nitroprusside; or combinations of the above-named drugs.

20. A method of treating hypertension which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a compound of claim 1.

21. An ophthalmological formulation for the treatment of ocular hypertension comprising an opthalmologically acceptable carrier and an effective ocular antihypertensive amount of a compound of claim 1.

22. A method of treating ocular hypertension comprising administering to a patient in need of such treatment an effective ocular antihypertensive amount of a compound of claim 1.

L14 ANSWER 48 OF 56 USPATFULL on STN
94:24299 Compositions and methods for improving cold tolerance in animals and humans.
Lee, Tze-Fun, Edmonton, Canada
Wang, Lawrence C. H., Edmonton, Canada
University of Alberta, Edmonton, Canada (non-U.S. corporation)
US 5296463 19940322
APPLICATION: US 1993-9995 19930127 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An orally ingestible composition for improving the cold tolerance of animals and humans which consists essentially of: (a) an **adenosine receptor antagonist** in an amount effective to improve the cold tolerance of said animals, said **antagonist** selected from the group of caffeine, theobromine, 8-phenyltheophylline, 8-cyclopentyltheophylline, 8-(4-(2-aminoethyl)amino carboxymethyloxyphenyl)-1,3-dipropylxanthine 8-(amino-4-chlorophenyl)-1,3-dipropylxanthine 8-(p-sulfophenyl)-1,3-dipropylxanthine, alone or mixed with two or more thereof, or in combination with theophylline or aminophylline or both; and (b) a nutritionally effective and cold tolerance improving amount of a nutritional supplement consisting of a mixture of 47 to 66% by weight of carbohydrate, 15 to 50% by weight of protein and 0 to 25% by weight of fat.

2. The composition according to claim 1, wherein the carbohydrate in the nutritional supplement mixture contains glucose, sucrose and starch in a weight ratio of about 1:3:6 to about 1:10:10.

3. A composition according to claim 1, wherein the mixture of carbohydrate, fat and protein comprises about 59.2%/w of carbohydrate, about 24.5%/w of fat and about 16.2%/w of protein.

4. A composition according to claim 1, wherein the **adenosine receptor antagonist** is theobromine.

5. A composition according to claim 4, wherein the protein is egg albumin.

6. A composition according to claim 1, for improving the cold tolerance of humans which includes as **adenosine receptor antagonist** theobromine in unit dosage form of about 2 to 4 mg/kg of body weight.

7. A composition according to claim 6, wherein the theobromine is in the form of cocoa powder containing 1-2%/w of theobromine.

8. A composition according to claim 1, wherein the nutritional supplement is a mixture of 50-60%/w of carbohydrate, 15-50%/w of protein and -25%/w of fat.

9. A composition according to claim 1, wherein the carbohydrate is a mixture of glucose, sucrose and corn starch.

10. A composition according to claim 9, wherein the protein is casein.

11. A composition according to claim 10, wherein the mixture of carbohydrate and protein comprises, about 53.8%/w of carbohydrate, 0%/w of fat and about 46.2%/w of protein.

L14 ANSWER 49 OF 56 USPATFULL on STN
94:20176 Macrocycles incorporating quinazolinones.
deLaszlo, Stephen E., Atlantic Highlands, NJ, United States
Glinka, Tomasz, Westfield, NJ, United States
Nachbar, Robert B., Washington Crossing, NJ, United States
Allen, Eric E., Somerset, NJ, United States
Prendergast, Kristine, Doylestown, PA, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
US 5292741 19940308
APPLICATION: US 1992-931749 19920818 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A compound of structural formula I: ##STR36## or a pharmaceutically acceptable salt thereof, wherein: Q is --N(R^4)-- or ##STR37## R^1 is a) aryl, b) C_{1-6} alkyl or C_{2-5} alkenyl, each of which is unsubstituted or substituted with aryl, C_{3-7} cycloalkyl, halo, CF_3 or CF_2CF_3, c) C_{3-7} cycloalkyl or d) perfluoro C_{1-4} alkyl; R^2 is C_{1-6} alkyl or F; R^3 is a) H, b) C_{1-6} alkyl, c) aryl, d) heteroaryl, e) C_{1-4} alkylamino, f) di(C_{1-4} alkyl)amino, g) (C_{1-6} alkoxy)CH_2 --, h) (C_{1-6} alkylthio)CH_2 --, i) C_{1-6} alkylthio, j) (C_{1-6} alkyl)$_2$ NCH_2 --, k) C_{2-6} alkenyl, l) C_{2-6} alkynyl, m) aryl C_{1-6} alkyl-, or n) C_{3-7} cycloalkyl; R^4 is a) --COR^6 wherein R^6 is 1) aryl, 2) heteroaryl, 3) morpholinyl, 4) piperazinyl, 5) N-(C_{1-4} alkyl)-piperazinyl, 6) N-(aryl)piperazinyl 7) C_{1-6} alkyl, or 8) substituted C_{1-6} alkyl or ##STR38## b) --CO_2 R^7 wherein R^7 is 1) C_{1-6} alkyl 2) substituted C_{1-6} alkyl, 3) aryl, or 4) heteroaryl; c) --$CONR^7$ R^8 wherein R^8 is C_{1-4} alkyl or H; d) C_{1-6} alkyl, e) substituted C_{1-6} alkyl, f) aryl, or g) heteroaryl; h) hydrogen, M is --N.dbd. or ##STR39## wherein R^9 is H, C_{1-3} alkyl, F or CF_3 ; K is --CO-- or --SO_2 --; L is --CO-- or --SO_2 -- A is --CO--, or --CH_2 --; D is --CH_2 --, --O--, --NR^8 or a single bond; E is $(CH_2)_b$ wherein b=0-6; G is (a) --$C(R^5)_2$ --, wherein the R^5 groups are the same or different and R^5 is C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl or hydrogen (b) --O--, (c) --$S(O)_p$ -- wherein p is 0-2, (d) --CH.dbd.CH--, (e) --CO--, (f) --NR^5 CO--, (g) --$NHSO_2$ NH--, (h) --CO_2 --, (i) --OCONH--, (j) --$NHCO_2$ --, (k) --NR^7, (l) aryl, (m) heteroaryl, or (n) single bond; J is (a) $(CH_2)_r$, wherein r is 1-8, or (b) single bond with the provisos that: 1) if A is CO then R^4 is C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl or H; 2) if A is CO and D is O or NR^8 then: (a) E is $(CH_2)_n$ wherein n is 2-6; (b) E is CH_2 and G is --$C(R^5)_2$ --; or (c) E is a single bond and G is aryl or heteroaryl; 3) if A is --(CH_2)--, then R^4 is --COR^6, --CO_2 R^7, --$CONR^7$ R^8 or H and D is --CH_2 -- or a single bond; 4) if Q is piperazine then A is CO wherein: aryl denotes phenyl or naphthyl, which can be unsubstituted or substituted with C_{1-3} alkyl, C_{1-3} alkoxy, halo, or CF_3 ; and heteroaryl means a 5- or 6-membered heteroaromatic comprising up to 3 heteroatoms selected from O, N and S selected from imidazole, pyrazole, triazole, thiazole, oxazole, thiadiazole, oxadiazole, oxathiazole, pyridine, pyrimidine, pyrazine, pyridazine, thiazine, wherein the heteroaromatic can be unsubstituted or substituted with one or two substituents selected from C_{1-3} alkyl, C_{1-3} alkoxy, halo or CF_3.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof wherein M is N.

3. The compound of claim 2 or a pharmaceutically acceptable salt thereof wherein L and K are independently --SO_2 or --CO--.

4. The compound of claim 3 or a pharmaceutically acceptable salt thereof wherein A is --CH_2 -- or --CO--.

5. The compound of claim 4 or a pharmaceutically acceptable salt thereof selected from the group consisting of the following compounds:

##STR40##

R^1	R^3	R^4	m	V	Y	
n-propyl	n-propyl	carbobenzyloxy	4	H_2	CH_2	
n-propyl	H	carbobenzyloxy	4	H_2	CH_2	
n-propyl	H	carbobenzyloxy	2	H_2	CH_2	
n-butyl	H	carbobenzyloxy	4	H_2	CH_2	
n-butyl	H	H	4	H_2	CH_2	
n-butyl	H	benzoyl	4	H_2	CH_2	
n-propyl	n-propyl	H	4	H_2	CH_2	
n-propyl	H	H	4	CO	NH	
n-butyl	H	H	3	CO	CH_2.	

6. A pharmaceutical composition useful in the treatment of hypertension which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 1.

7. The composition of claim 6 which includes another antihypertensive selected from a diuretic selected from hydrochlorothiazide, chlorothiazide, chlorthalidone, methyclothiazide, furosemide, ethacrynic acid, triamterene, amiloride and spironolactone; a calcium channel blocker, selected from diltiazem, felodipine, nifedipine, nitrendipine and verapamil; a β-adrenergic **antagonist** selected from timolol, atenolol, metoprolol, propanolol, nadolol and pindolol; an angiotensin converting enzyme inhibitor selected from enalapril, lisinopril, captopril, ramipril, quinapril and zofenopril; a renin inhibitor selected from A-69729 and FK 744; an α-adrenergic **antagonist** selected from prazosin, doxazosin, and terazosin; a sympatholytic agent selected from methyldopa, clonidine and guanabenz; the atriopeptidase inhibitor, UK-79300; the serotonin **antagonist**, ketanserin; the A_2 -**adenosine receptor** agonist CGS 22492C; a potassium channel agonist selected from pinacidil and cromakalim; or another antihypertensive drug selected from reserpine, minoxidil, guanethidine, hydralazine hydrochloride and sodium nitroprusside; or combinations of the above-named drugs.

8. A method of treating hypertension which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a compound of claim 1.

9. An ophthalmological formulation for the treatment of ocular hypertension comprising an ophthalmologically acceptable carrier and an

effective ocular antihypertensive amount of a compound of claim 1.

10. A method of treating ocular hypertension comprising administering to a patient in need of such treatment an effective ocular antihypertensive amount of a compound of claim 1.

L14 ANSWER 50 OF 56 USPATFULL on STN
93:89407 Composition for determining viability of tissue.
McAfee, Donald A., Richmond, VA, United States
Belardinelli, Luiz, Gainesville, FL, United States
Whitby Research, Inc., Richmond, VA, United States (U.S. corporation)
US 5256398 19931026
APPLICATION: US 1992-828115 19920130 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition comprising adenosine or an adenosine agonist in combination with an A_1 **adenosine receptor antagonist** in an amount sufficient to alleviate all effects of adenosine or said adenosine agonist except coronary vasodilation when said composition is administered to a mammal.

2. The composition of claim 1 wherein the A_1 **adenosine receptor antagonist** is ##STR4## wherein R_1 is hydrogen or R_2 ; R_2 is selected from the group consisting of endo-2-norbornyl or cyclopentyl; R_3 is selected from the group consisting of hydrogen, halogen, amine, carboxy, alkyl radicals having 1 to 10 carbon atoms, cycloalkyl radicals having from 3 to 8 ring carbon atoms, thio, sulfonate, sulfonamide, sulfone, sulfoxamide, phenyl, alkyl-substituted amine, and cycloalkyl substituted amine; R_4 is selected from the group consisting of benzyl, phenyl, alkyl groups comprising from 1 to 4 carbon atoms, alkyl ether groups comprising from 1 to 4 carbon atoms, and alkyl alcohols comprising from 1 to 4 carbon atoms; and R_5 is selected from the group consisting of hydrogen, hydroxy, sulfonate, halogen, alkoxy and cycloalkoxy groups comprising 1 to 6 carbon atoms.

3. The composition of claim 1 wherein the A_1 **adenosine receptor antagonist** is selected from the group consisting of: N^6 -(endo-2-norbornyl)-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-bromo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-amino-9-methyl adenine, N^6 -(endo-2-norbornyl)-9-[(2-hydroxyethoxy)methyl]adenine, N^6 -(endo-2-norbornyl)-8-thio-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-oxo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-amine-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-9-methyl adenine, and N^6 -(exo-2-norbornyl)-9-methyl adenine.

4. The composition of claim 3 wherein the A_1 **adenosine receptor antagonist** is selected from the group consisting of N^6 -3-pentyl-9-methyl adenine, N^6 -cyclopentyl-9-methyl adenine, N^6 -1-(2-thienyl)-2-butyl-9-methyl adenine, and N^6 -cyclopentyl-8-cyclopentyl-9-methyl adenine.

5. The composition of claim 1 wherein the A_1 **adenosine receptor antagonist** is selected from the group consisting of N^6 -3-pentyl-9-methyl adenine, N^6 -cyclopentyl-9-methyl adenine, N^6 -1-(2-thienyl)-2-butyl-9-methyl adenine, and N^6 -cyclopentyl-8-cyclopentyl-9-methyl adenine.

6. The composition of claim 4 wherein said derivative is 9-methyl-N^6 -endo-norbornyl adenine.

7. A composition comprising adenosine or an adenosine **antagonist** in combination with an A_1 **adenosine receptor antagonist** in an amount sufficient to reduce the amount of adenosine or said adenosine agonist necessary to dilate a vascular circulation system when said composition is administered to a mammal.

8. The composition of claim 7 wherein the A_1 **adenosine receptor antagonist** is ##STR5## wherein R_1 is hydrogen or R_2 ; R_2 is selected from the group consisting of endo-2-norbornyl or

cyclopentyl; R_3 is selected from the group consisting of hydrogen, halogen, amine, carboxy, alkyl radicals having 1 to 10 carbon atoms, cycloalkyl radicals having from 3 to 8 ring carbon atoms, thio, sulfonate, sulfonamide, sulfone, sulfoxamide, phenyl, alkyl-substituted amine, and cycloalkyl substituted amine; R_4 is selected from the group consisting of benzyl, phenyl, alkyl groups comprising from 1 to 4 carbon atoms, alkyl ether groups comprising from 1 to 4 carbon atoms, and alkyl alcohols comprising from 1 to 4 carbon atoms; and R_5 is selected from the group consisting of hydrogen, hydroxy, sulfonate, halogen, alkoxy and cycloalkoxy groups comprising 1 to 6 carbon atoms.

9. The composition of claim 7, wherein the A_1 **adenosine receptor antagonist** is an N^6 -norbornyl substituted adenine.

10. The composition of claim 7 wherein the A_1 **adenosine receptor antagonist** is selected from the group consisting of: N^6 -(endo-2-norbornyl)-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-bromo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-amino-9-methyl adenine, N^6 -(endo-2-norbornyl)-9-[(2-hydroxyethoxy)methyl]adenine, N^6 -(endo-2-norbornyl:,-8-thio-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-oxo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-amine-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-9-methyl adenine, and N^6 -(exo-2-norbornyl)-9-methyl adenine.

11. The composition of claim 7 wherein the A_1 **adenosine receptor antagonist** is selected from the group consisting of N^6 -3-pentyl-9-methyl adenine, N^6 -cyclopentyl-9-methyl adenine, N^6 -1-(2-thienyl)-2-butyl-9-methyl adenine, and N^6 -cyclopentyl-8-cyclopentyl-9-methyl adenine.

12. The composition of claim 10 wherein said derivative is 9-methyl-N^6 -endo-norbornyl adenine.

L14 ANSWER 51 OF 56 USPATFULL on STN
93:80750 Methods for increasing arousal and alertness and for the amelioration of comatose states.
Costa, Jonathan L., Wheaton, IL, United States
Salazar, Hernan V., Cali, Colombia
Diazgranados, Jesus A., Cali, Colombia
Fractal Laboratories, Inc., Newton, NJ, United States (U.S. corporation)
US 5248678 19930928
APPLICATION: US 1992-906585 19920630 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of increasing the arousal and alertness of comatose patients or near-comatose patients comprising concomitantly administering to the patients effective amounts of an **adenosine receptor antagonist** and a GABA agonist.

2. The method of claim 1 wherein the **adenosine receptor antagonist** is administered first.

3. The method of claim 1 wherein the GABA agonist is administered first.

4. The method of claim 1 wherein the **adenosine receptor antagonist** and the GABA agonist are administered simultaneously.

5. The method of claim 1 wherein the **adenosine receptor antagonist** is selected from the group consisting of caffeine, theophylline, 8-phenyltheophylline (8-PT), 8-cyclopentyltheophylline (CPT) and its 1, 3-dipropyl homolog (CPX), the p-$PhOCH_2$ $CONHCH_2$ NH_2 analog of CPX(XAC), the p -$PhSO_2$ $NMeCH_2$ CH_2 NMe_2 analog of CPX (PD115,199), CGS15,943 represented by the formula ##STR4## and compounds represented by the formula ##STR5## and the pharmaceutically acceptable acid addition salts thereof, whereinX and X^1 are each selected from the group consisting of hydrogen, fluorine, chlorine, bromine and methoxy; R_1 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl and phenyl; and R_2 and

R_3 are each selected from the group consisting of hydrogen, lower alkyl, phenylalkyl having up to three carbon atoms in the alkyl moiety and alkanoyl having from two to five carbon atoms, provided that at least one of R_2 and R_3 is always other than hydrogen when X and X^1 are each hydrogen and R_1 is hydrogen or methyl; or R_2 and R_3, when taken together, complete a piperazine ring.

6. The method of claim 1 wherein the GABA agonist is selected from the group consisting of the avermectins diazepam, chlordiazepoxide, flurazepam, nitrazepam, oxazepam, medazepam, chlorazepate di-potassium, demoxepam, prazepam, temazepam, quazepam, clonazepam, flunitrazepam, oxazolazepam, ketazolapam, tetrazepam, bromazepam, lorprazolam, lorazepam, halazepam, alprazolam, midazolam, triazolam, trifluadom, ##STR6## and lormetazepam, and baclofen, isoniazid, L-threonine, vigabatrin, gabapentin, valproic acid, zonisamide, muscimol and progabide.

7. The method of claim 1 wherein the **adenosine receptor antagonist** is theophylline and the GABA agonist is ivermectin.

8. The method of claim 1 wherein the **adenosine receptor antagonist** is theophylline and the GABA agonist is diazepam.

9. The method of claim 1 wherein the **adenosine receptor antagonist** is aminophylline and the GABA agonist is ivermectin.

10. The method of claim 1 wherein the **adenosine receptor antagonist** is aminophylline and the GABA agonist is diazepam.

L14 ANSWER 52 OF 56 USPATFULL on STN
93:35690 8-substituted purines as selective **adenosine receptor** agents.
Peet, Norton P., Cincinnati, OH, United States
Lentz, Nelsen L., West Chester, OH, United States
Dudley, Mark W., Somerville, OH, United States
Merrell Dow Pharmaceuticals Inc., Cincinnati, OH, United States (U.S. corporation)
US 5208240 19930504
APPLICATION: US 1991-667943 19910312 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of the formula ##STR36## wherein R_1, R_2 and R_3 are each independently a C_1 -C_4 alkyl, m is an integer 0, 1 or 2, A is O or S, n is an integer 1, 2 or 3, and R_4 is H or a C_1 -C_4 alkyl.

2. A compound of the formula ##STR37## wherein R_1, R_2 and R_3 are each independently a C_1 -C_4 alkyl, m is an integer 0, 1 or 2, A is O or S, n is an integer 1, 2 or 3, Y is --$NH(CH_2)_p$ NH--, p is an integer 2, 3 or 4 Z is a radical of the formula ##STR38## q is an integer 0, 1, 2 or 3, and R_5 is a radical selected each time taken from the group consisting of H, CH_3, --$CH(CH_3)_2$, --$CH(CH_3)CH_2$ CH_3, --CH_2 $CH(CH_3)_2$, --CH_2 CH_2 CH_2 NH_2, --CH_2 CH_2 CH_2 CH_2 NH_2, --CH_2 CH_2 CH_2 N.dbd.$C(NH_2)_2$, --CH_2 CH_2 CH_2 CH_2 N.dbd.$C(NH_2)_2$, ##STR39##

3. A compound of the formula ##STR40## wherein R_1, R_2 and R_3 are each independently a C_1 -C_4 alkyl, m is an integer 0, 1 or 2, A is O or S, n is an integer 1, 2 or 3, Z is a radical of the formula ##STR41## q is an integer 1, 2 or 3, and R_5 is a radical selected each time taken from the group consisting of H, CH_3, --$CH(CH_3)_2$, --$CH(CH_3)CH_2$ CH_3, --CH_2 $CH(CH_3)_2$, --CH_2 CH_2 CH_2 NH_2, --CH_2 CH_2 CH_2 NH_2, --CH_2 CH_2 CH_2 N.dbd.$C(NH_2)_2$, --CH_2 CH_2 CH_2 CH_2 N.dbd.$C(NH_2)_2$, ##STR42##

4. A method of providing a selective A_1 -**adenosine receptor antagonist** effect in a patient in need thereof comprising administering to said patient a therapeutically effective A_1

-**antagonistic** amount of a compound of claim 1, 2 or 3.

5. A method according to claim 4 wherein the patient is in need of treatment for Alzheimer's Disease.

6. A method according to claim 4 wherein the patient is in need of. treatment for congestive heart failure.

7. A method according to claim 4 wherein the patient is in need of treatment for pulmonary bronchoconstriction.

8. A composition comprising an assayable amount of a compound of claim 1, 2 or 3 in admixture or otherwise in association with an inert carrier.

9. A pharmaceutical composition comprising an effective immunosuppressive amount of a compound of claim 1, 2 or 3 in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

10. A compound according claim 2 wherein the compound is N-(2-Aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

11. A compound according claim 2 wherein the compound is N-(2-Aminoethyl)-2-[4-[1-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

12. A compound according to claim 2 wherein the compound is (+)-N-(2-aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

13. A compound according to claim 2 wherein the compound is (-)-N-(2-aminoethyl)-2-[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]-acetamide.

L14 ANSWER 53 OF 56 USPATFULL on STN
93:29200 Quinazolinone and pyridopyrimidine a-II **antagonists**.
Allen, Eric E., Edison, NJ, United States
Olson, Richard E., Wilmington, DE, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)E. I. du Pont de Nemours and Company, Wilmington, DE, United States (U.S. corporation)
US 5202322 19930413
APPLICATION: US 1991-765626 19910925 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of structural formula: ##STR107## or a pharmaceutically acceptable salt thereof, wherein: G is (1) R^1 or ##STR108## E is (1) a single bond, (2) --CH(OH)--, (3) --O--, (4) --CO--, (5) $--S(O)_x(CH_2)_s$ --wherein x is 0, 1, or 2, and s is 0-5, or (6) $--NR^3(CH_2)_s$ -- wherein R^3 is (a) --H, (b) C_{2-4} alkanoyl, (c) C_{1-6} alkyl, (d) C_{2-6} alkenyl, (e) C_{3-7} cycloalkyl, (f) phenyl, or (g) benzyl; R is (1) aryl, (2) heteroaryl, (3) C_{3-7} cycloalkyl, (4) polyfluoro-C_{1-4} alkyl, (5) --H, (6) C_{2-6} alkenyl, (7) C_{2-6} alkynyl, (8) C_{1-6} alkyl, either unsubstituted or substituted with: (a) aryl, (b) C_{3-7} cycloalkyl, (c) halo, (d) $--NH_2$, (e) $--NH(C_{1-4}$ alkyl), (f) $--N(C_{1-4}$ alkyl$)_2$, (g) $--OR^4$, wherein R^4 is (i) --H, (ii) aryl, (iii) heteroaryl, (iv) C_{1-6} alkyl, or (v) aryl-C_{1-6} alkyl; (h) $--COOR^4$, (i) $--NHSO_2R^4$, or (j) $--SO_2NHR^5$, wherein R^5 is (i) --H (ii) C_{1-5} alkyl, (iii) aryl or (iv) $--CH_2$ --aryl; R^1 is (1) $--CO_2R^4$ (2) $--SO_3R^6$, wherein R^6 is (a)--H (b)--$CH(R^4)$--O--CO--R^{4a} wherein R^{4a} is (i) C_{1-6} alkyl, (ii) aryl or (iii) $--CH_2$ --aryl; (3) $--P(O)(OR^6)_2$, (4) --$CONHNHSO_2CF_3$, (5) $--SO_2NHCN$, (6) $--P(O)(OR^6)(OR^4)$, (7) $--SO_2NHR^7$, wherein R^7 is (a) --H (b) aryl, (c) heteroaryl, (d) C_{3-7} cycloalkyl, (e) polyfluoro-C_{1-4} alkyl, or (f) C_{1-10} alkyl, either unsubstituted or substituted with: (i) aryl, (ii) heteroaryl, (iii) --OH, (iv) --SH, (v) C_{1-4} alkoxy, (vi) C_{1-4} alkylthio (vii) halo (viii) $--NO_2$ (ix) $--CO_2$

R^{11}, wherein R^{11} is --H or C_{1-4} alkyl, (x) --NH_2, (xi) --$NH(C_{1-4}$ alkyl) (xii) --$N(C_{1-4}$ alkyl)$_2$ (xiii) --PO_3H_2, (xiv) --$P(O)(OH)(OC_{1-4}$ alkyl), or (xv) --$P(O)(OR^4)(R^8)$ wherein R^8 is (a) --H (b) --C_{1-5} alkyl, (c) -aryl or (d) --CH_2 --aryl, (8) --$NHSO_2R^7$, (9) --SO_2NHCOR^7, (10) --$CH_2SO_2NHCOR^7$, (11) --$CONHSO_2R^7$, (12) --$CH_2CONHSO_2R^7$, (13) --$NHSO_2NHCOR^7$, (14) --$NHCONHSO_2R^7$, (15) --$SO_2NHCONR^4R^7$, (16) --$CH_2SO_2NHR^7$, (17) --$C(OH)(R^8)$--$P(O)(OR^6)_2$, (18) --$P(O)(R^8)(OR^6)$, (19) tetrazol-5-yl, substituted with R^9 wherein R^9 is (a) --H, (b) C_{1-6} alkyl, (c) C_{2-4} alkenyl, (d) C_{1-4} alkoxy-C_{1-4} alkyl (e) benzyl, either unsubstituted or substituted with (i) --NO_2, (ii) --NH_2, (iii) --OH, or (iv) --OCH_3, (20) --CH_2 -tetrazol-5-yl substituted with R^9, (21) --CONH-tetrazol-5-yl substituted with R^9, (22) --1,3,4-triazol-2-yl substituted with R^{10} wherein R^{10} is (a) --CN, (b) --NO_2, (c) --CF_3 or (d) --CO_2R^4 ; (23) 1,2,3-triazol-4-yl substituted with R^{10}, (24) --$SO_2NHSO_2R^7$, (25) --OH or ##STR109## R^2 is: (1) --H, (2) --CO-aryl, (3) C_{3-7} cycloalkyl, (4) halo, (5) --OH, (6) --OR^7 (7) polyfluoro-C_{1-4} alkyl, (8) --$S(O)_xR^7$, (9) --$COOR^4$, (10) --SO_2H, (11) --NR^4R^7, (12) --$NHCOR^7$, (13) --$NHCO_2R^7$ (14) --$SO_2NR^8R^{11}$, wherein R^{11} is (a) --H or (b) C_{1-4} alkyl, (15) --NO_2 (16) --$NHSO_2R^7$ (17) --$NHCONR^4R^7$, (18) --$OCONR^7R^8$, (19) aryl, (20) heteroaryl, (21) --$NHSO_2$ polyfluorophenyl, (22) --SO_2NH--heteroaryl, (23) --SO_2NHCOR^7, (24) --$CONHSO_2R^7$, (25) --$PO(OR^4)_2$, (26) --$PO(OR^4)R^8$, (27) tetrazol-5-yl, (28) --CONH(tetrazol-5-yl), (29) --COR^4 (30) --SO_2NHCN, (31) --CO--heteroaryl, (32) --$NHSO_2NR^7R^8$, or (33) C_{1-6} alkyl, either unsubstituted or substituted with (a) --OH, (b) --guanidino, (c) --C_{1-4} alkoxy, (d) --$N(R^4)_2$, (e) --CO_2R^4, (f) --$CON(R^4)_2$, (g) --O--COR^4 (h) -aryl, (i) -heteroaryl, (j) --$S(O)_xR^7$ (k) -tetrazol-5-yl, (l) --$CONHSO_2R^7$, (m) --SO_2NH--heteroaryl, (n) --SO_2NHCOR^7, (o) --$PO(OR^4)_2$, (p) --$PO(OR4)R^9$, (q) --SO_2,NHCN, (r) --$NR^{11}COOR^7$, (s) -morpholino, (t) --N(C_{1-6} alkyl)piperazine or (u) --COR^4, with the proviso that the R^2 groups can be the same or different; or two R^2 groups joined to the same carbon taken together represent (a) =O (b) =S or (c) --[$(CH_2)_{2-6}$]--; R^{2a}, R^{2b}, R^{3a} and R^{3b} independently represent (1) C_{1-5} alkyl, (2) polyfluoro-C_{1-5} alkyl, (3) halo; (4) hydroxy or (5) C_{1-5} alkoxy; U, V and W are --CH.dbd. or Z is: (1) --O--, (2) --$S(O)_x$ -- (3) --$N(R^{12})$-- wherein R^{12} is (a) --H or (b) --R^{13} wherein R^{13} is (i) C_{1-4} alkyl, (ii) C_{3-7} cycloalkyl (iii) aryl, (iv) heteroaryl, (v) polyfluoro-C_{1-4} alkyl, (vi) polyfluoro-C_{3-7} cycloalkyl, or (vii) polyfluorophenyl; (4) --$N(COR^{13})$--, (5) --$N(CONHR^{13})$--, (6) --$N(CON(R^{13})_2)$--, (7) --$N(CO_2R^{13})$--, (8) --$N(SO_2NHR^{13})$--, (9) --$N(SO_2N(R^{13})_2)$--, (10) --$N(SO_2R^{13})$--, or (11) --$C(R^2)_2$ --, X is (1) a single bond (2) --SO_2 -- (3) --O-- (4) --$C(R^2)_2$ -- (5) --$N(R^{12})$-- (6) --$N(COR^{13})$-- (7) --$N(CONHR^{13})$-- (8) --$N(CON(R^{13})_2)$-- (9) --$N(CO_2R^{13})$-- (10) --$N(SO_2NHR^{13})$-- (11) --$N(SO_2N(R^{13})2)$-- (12) --$N(SO_2R^{13})$-- Y is (1) --O-- (2) --$S(O)_x$ -- where x is 0, 1, or 2, (3) --$C(R^2)_2$ -- (4) --$N(R^{12})$-- (5) --$N(COR^{13})$-- (6) --$N(CONHR^{13})$-- (7) --$N(CON(R^{13})_2)$-- (8) --$N(CO_2R^{13})$-- (9) --$N(SO_2NHR^{13})$-- (10) --$N(SO_2N(R^{13})_2)$-- (11) --$N(SO_2R^{13})$--.

2. The compound of claim 1 wherein G is ##STR110##

3. The compound of claim 2 wherein: E is (1) a single bond, (2) --O-- or (3) --S--; R is (1) C_{1-6} alkyl, either unsubstituted or substituted with: (a) C_{3-5} cycloalkyl, (b) --Cl, (c) --CF_3, (d) --OCH_3, (e) --OC_2H_5, (f) --SCH_3, (g) --SC_2H_5 (h) --F, or (i) phenyl; (2) C_{2-5} alkenyl, (3) C_{2-5} alkynyl, or (4) C_{3-5} cycloalkyl; R^1 is (1) --CO_2H, (2) tetrazol-5-yl, (3) --$NHSO_2R^7$, (4) --SO_2NH--heteroaryl,

(5) --CH_2 SO_2 NH-heteroaryl, (6) --SO_2 $NHCOR^7$, (7) --CH_2 SO_2 $NHCOR^7$, (8) --$CONHSO_2$ R^7, (9) --CH_2 $CONHSO_2$ R^7 (10) --$_2$ $NHSO_2$ $NHCOR^7$ or (11) --$NHCONHSO_2$ R^7 (12) --SO_2 $NHCON(R^4)R^7$ (13) --SO_2 NHCON Z R^2 is: (1) H, (2) C_{1-4} alkyl, either unsubstituted or substituted with: (a) --CO_2 R^4, (b) --$OCOR^{4a}$, (c) --OH, or (d) --aryl; (3) C_{2-4} alkenyl, (4) --OH, (5) -NO_2, (6) -$NHCOR^7$, (7) --C_{1-4} alkoxy, (8) --$NHCO_2$ R^7, (9) --NR^4 R^7 or (10) --Cl, --F, or --Br; or two R^2 groups on the same carbon taken together represent .dbd.O or --$(CH_2)_{2-5}$ --; and X is (1) --$C(R^2)_2$ -- or (2) a single bond; Y is (1) --$C(R^2)_2$ -- or (2) --$N(R^{12})_2$ --; Z is (1) --$N(R^{12})$--, (2) --$N(COR^{13})$--, (3) --$N(CONHR^{13})$--, or (4) --$N(CON(R^{13})_2)$--, (5) --O-- (6) --S--.

4. The compound of claim 3 of structural formula: ##STR111## or a pharmaceutically acceptable salt thereof selected from the group of compounds consisting of those in the following table:

RE	R^1	Z
n-C_4 H_9	##STR112##	O
n-C_4 H_9	##STR113##	##STR114##
n-C_3 H_7	##STR115##	##STR116##
n-C_3 H_7	##STR117##	##STR118##
n-C_3 H_7	##STR119##	##STR120##
n-C_4 H_9	##STR121##	##STR122##

5. The compound of claim 1 wherein G is R^1.

6. The compound of claim 5 wherein: E is (1) a single bond, (2) --O-- or (3) --S--; R is (1) C_{1-6} alkyl, either unsubstituted or substituted with: (a) C_{3-5} cycloalkyl, (b) --Cl, (c) --CF_3, (d) --OCH_3, (e) --OC_2 H_5, (f) --SCH_3, (g) --SC_2 H_5 (h) --F, or (i) phenyl; (2) C_{2-5} alkenyl, (3) C_{2-5} alkynyl, or (4) C_{3-5} cycloalkyl; R^1 is (1) --CO_2 H, (2) tetrazol-5-yl, (3) --$NHSO_2$ R^7, (4) --SO_2 NH-heteroaryl, (5) --CH_2 SO_2 NH-heteroaryl, (6) --SO_2 $NHCOR^7$, (7) --CH_2 SO_2 $NHCOR^7$, (8) --$CONHSO_2$ R^7, (9) --CH_2 $CONHSO_2$ R^7 (10) --$_2$ $NHSO_2$ $NHCOR^7$ or (11) --$NHCONHSO_2$ R^7 (12) --SO_2 $NHCON(R^4)R^7$ (13) --SO_2 NHCON Z R^2 is: (1) H, (2) C_{1-4} alkyl, either unsubstituted or substituted with: (a) --CO_2 R^4, (b) --$OCOR^{4a}$, (c) --OH, or (d) -aryl; (3) C_{2-4} alkenyl, (4) --OH, (5) --NO_2, (6) --$NHCOR^7$, (7) --C_{1-4} alkoxy, (8) --$NHCO_2$ R^7, (9) --NR^4 R^7 or (10) --Cl, --F, or --Br; or two R^2 groups on the same carbon taken together represent .dbd.O; and X is (1) --$C(R^2)_2$ -- or (2) a single bond; Y is (1) --$C(R^2)_2$ -- or (2) --$N(R^{12})_2$ --; Z is (1) --$N(R^{12})$--, (2) --$N(COR^{13})$--, (3) --$N(CONHR^{13})$--, or (4) --$N(CON(R^{13})_2)$--, (5) --O-- (6) --S--.

7. The compound of claim 6 wherein E-R is ##STR123##

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

9. The composition of claim 8 which includes another antihypertensive selected from a diuretic selected from hydrochlorothiazide,

chlorothiazide, chlorthalidone, methyclothiazide, furosemide, ethacrynic acid, triamterene, amiloride, atriopeptin and spironolactone; a calcium channel blocker, selected from diltiazem, felodipine, nifedipine, amlodipine, rumodipine, isradapine, nitrendipine and verapamil; a β-adrenergic **antagonist** selected from timolol, atenolol, metoprolol, propanolol, nadolol and pindolol; an angiotensin converting enzyme inhibitor selected from enalapril, lisinopril, captopril, ramipril, quinapril and zofenopril; a renin inhibitor selected from A-69729, FK-906 and FK-744; an α-adrenergic **antagonist** selected from prazosin, doxazosin, and terazosin; a sympatholytic agent selected from methyldopa, clonidine and guanabenz; the atriopeptadase inhibitor UK-79300 (alone or with ANP); the serotonin **antagonist**, ketanserin; the A_2 -**adenosine receptor** agonist CGS 22492C; a potassium channel agonist selected from pinacidil and cromakalim; another antihypertensive drug selected from reserpine, minoxidil, guanethidine, hydralazine, hydrochloride and sodium nitroprusside; a cardiac stimulant selected from dobutamine and xamoterol; a phosphodiesterase inhibitor selected from amrinone and milrinone or combinations of the above-named drugs.

10. A method of treating hypertension which comprises administering to a patient in need of such treatment a pharmaceutically effective amount of a compound of claim 1.

11. An ophthalmological formulation for the treatment of ocular hypertension comprising an ophthalmologically acceptable carrier and an effective ocular antihypertensive amount of a compound of claim 1.

12. A method of treating ocular hypertension comprising administering to a patient in need of such treatment an effective ocular antihypertensive amount of a compound of claim 1.

L14 ANSWER 54 OF 56 USPATFULL on STN
93:18646 Compositions and methods for improving cold tolerance in animals and humans.
Lee, Tze-Fun, Edmonton, Canada
Wang, Lawrence C., Edmonton, Canada
University of Alberta, Edmonton, Canada (non-U.S. corporation)
US 5192740 19930309
APPLICATION: US 1991-700320 19910509 (7)
PRIORITY: GB 1987-29714 19871221
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of improving the cold tolerance of animals and humans which comprises administering to an animal or human in need thereof an orally ingestible composition consisting essentially of an **adenosine receptor antagonist** selected from the group of caffeine, theobromine, 8-phenyltheophylline, 8-cyclopentyltheophylline, 8-(4-(2-aminoethyl)amino carboxymethyloxyphenyl)-1,3-dipropylxanthine, 8-(amino-4-chlorophenyl)-1,3-dipropyl xanthine, and 8-(p-sulfophenyl)-1,3-dipropyl xanthine, alone or mixed with two or more thereof, or in combination with theophylline or aminophylline or both, and a nutritional supplement mixture of 47 to 66% by weight of carbohydrate, 15-50% by weight of protein and 0 to 25% by weight of fat, said composition administered in an amount sufficient to improve the cold tolerance of said animal or human.

2. The method according to claim 1, wherein said **adenosine receptor antagonist** is theobromine.

3. The method according to claim 1, wherein said **adenosine receptor antagonist** is caffeine.

4. The method according to claim 1, wherein said **adenosine receptor antagonist** is 8-phenyltheophylline.

5. The method according to claim 1, wherein said **adenosine receptor antagonist** is 8-cyclopentyltheophylline.

6. The method according to claim 1, wherein said **adenosine receptor antagonist** is 8-(4-(2-aminoethyl)aminocarboxymethyloxyphenyl)-1,3-dipropylxanthine.

7. The method according to claim 1, wherein said **adenosine receptor antagonist** is 8-(amino-4-chlorophenyl)-1,3-dipropylxanthine.

8. The method according to claim 1, wherein said **adenosine receptor antagonist** is 8-(p-sulfophenyl)-1,3-dipropylxanthine.

9. The method according to claim 1, wherein said **adenosine receptor antagonist** is a mixture of 8-phenyltheophylline and aminophylline.

10. The method according to claim 1, wherein the carbohydrate in the nutritional supplement mixture contains glucose, sucrose and starch in a weight ratio of about 1:3:6 to about 1:10:10.

11. The method according to claim 1, wherein the carbohydrate is a sugar.

12. The method according to claim 11, wherein the sugar is selected from sucrose and glucose.

13. The method according to claim 1, wherein the carbohydrate is starch.

14. The method according to claim 1, wherein the carbohydrate is a mixture of a sugar and starch.

15. The method according to claim 14, wherein the carbohydrate is a mixture of glucose, sucrose and starch.

16. The method according to claim 15, wherein the weight ratio of glucose to sucrose to starch is about 1:3:6.4, wherein 1=0.26 g.

17. The method according to claim 15, wherein the weight ratio of glucose to sucrose to starch is about 1:5:10.6, wherein 1=0.26 g.

18. The method according to claim 14, wherein the **adenosine receptor antagonist** is theobromine.

19. The method according to claim 15, wherein the **adenosine receptor antagonist** is theobromine.

20. The method according to claim 16, wherein the **adenosine receptor antagonist** is theobromine.

21. The method according to claim 17, wherein the **adenosine receptor antagonist** is theobromine.

22. The method according to claim 1, wherein the carbohydrate is a sugar.

23. The method according to claim 1, wherein the carbohydrate is a mixture of a sugar and starch.

24. The method according to claim 23, wherein the carbohydrate is a mixture of glucose, sucrose and starch.

25. The method according to claim 24, wherein the **adenosine receptor antagonist** is theobromine.

26. The method according to claim 25, wherein the protein is egg albumin and wherein the fat is corn oil.

27. The method according to claim 26, wherein the mixture comprises glucose:sucrose:starch:egg albumin:corn oil in a weight ratio of about 1:3:6.4:5:0.33.

28. The method according to claim 1, wherein the **adenosine receptor antagonist** is theobromine in an amount of about 2 to 4 mg/kg of body weight.

29. The method according to claim 28, wherein the theobromine is in the form of cocoa powder containing 1-2% by weight of theobromine in said powder.

30. The method according to claim 1, wherein the nutritional supplement is a mixture of 50-60% by weight of carbohydrate, 15-50% by weight of protein and 0-25% by weight of fat.

31. The method according to claim 30, wherein the carbohydrate is a mixture of sucrose and corn syrup solids.

32. The method according to claim 31, wherein the protein is a mixture of casein and soya protein isolates.

33. The method according to claim 32, wherein the fat is oil.

34. The method according to claim 33, wherein the mixture of carbohydrate, fat and protein comprises, about 59.2% by weight of corn syrup solids and sucrose, about 24.5% by weight of corn oil, and about 16.2% by weight of casein and soya protein isolates.

35. The method according to claim 30, wherein the carbohydrate is a mixture of glucose, sucrose and corn starch.

36. The method according to claim 35, wherein the protein is casein.

37. The method according to claim 36, wherein the amount of theobromine is about 2 mg/kg of body weight.

38. The method according to claim 37, wherein the nutritional supplement comprises about 53% by weight of carbohydrate and about 46.2% by weight of protein.

L14 ANSWER 55 OF 56 USPATFULL on STN
92:43977 Method of determining viability of tissue.
McAfee, Donald A., Richmond, VA, United States
Belardinelli, Luiz, Gainesville, FL, United States
Whitby Research, Inc., Richmond, VA, United States (U.S. corporation)
US 5117830 19920602
APPLICATION: US 1990-610544 19901108 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for determining the viability of tissue in a region of an organism having a vascular circulatory system that supplies blood to said region which comprises the steps of: (a) dilating said vascular circulation system by introducing adenosine or an adenosine agonist into said vascular circulation system in order to increase the flow of blood into said region; (b) introducing a blood flow marking medium into said region; (c) alleviating the non-dilating effects of adenosine or said adenosine agonist by introducing an A_1 **adenosine receptor antagonist** into said vascular circulatory system; and (d) determining the amount of marking medium in said region.

2. The method of claim 1 wherein the A_1 **adenosine receptor** agonist is ##STR4## wherein R_1 is hydrogen or R_2 ; R_2 is selected from the group consisting of endo-2-norbornyl or cyclopentyl; R_3 is selected from the group consisting of hydrogen, halogen, amine, carboxy, alkyl radicals having 1 to 10 carbon atoms, cycloalkyl radicals having from 3 to 8, preferably 5 to 6, ring carbon atoms, thio, sulfonate, sulfonamide, sulfon, sulfoxamide, phenyl, alkyl-substituted amine, and cycloalkyl substituted amine; is selected from the group consisting of benzyl, phenyl, and alkyl groups comprising from 1 to 4 carbon atoms, wherein said alkyl group can be substituted with oxygen, for instance ethers and alcohols; and R_5 is selected from the group consisting of hydrogen; hydroxy; sulfonate; halogen; alkoxy and cycloalkoxy groups comprising 1 to 6 carbon atoms.

3. The method of claim 1 wherein the A_1 **adenosine receptor** agonist is an N^6 -norbornyl substituted adenine.

4. The method of claim 3 wherein the A_1 **adenosine receptor** agonist is selected from the group consisting of: N^6 -(endo-2-norbornyl)-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-bromo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-amino-9-methyl adenine, N^6 -(endo-2-norbornyl)-9-[(2-hydroxyethoxy)methyl]adenine, N^6 -(endo-2-norbornyl)-8-thio-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-oxo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-amine-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-

cyclopentyl-9-methyl adenine, and N^6 -(exo-2-norbornyl)-9-methyl adenine.

5. The method of claim wherein the A_1 **adenosine receptor** agonist is selected from the group consisting of N^6 -3-pentyl-9-methyl adenine, N^6 -cyclopentyl-9-methyl adenine, N^6 -1-(2-thienyl)-2-butyl-9-methyl denine, and N^6 -cyclopentyl-8-cyclopentyl-9-ethyl adenine.

6. The method of claim 1 wherein said marking medium is selected from the group consisting of thallium-201 and rubidium-82.

7. The method of claim 6 wherein said marking medium comprises thallium-201.

8. The method of claim 7 wherein adenosine is introduced into said vascular circulatory system.

9. The method of claim 8 wherein the amount of marking medium in said region is determined by non-invasive myocardial imaging of the blood flow to said region.

10. The method of claim 3 wherein said N^6 -norbornyl substituted adenine is N^6 -(endo-norbornyl)-9-methyl adenine.

11. A method for determining the viability of tissue in a region of an organism having a vascular circulatory system that supplies blood to said region which comprises the steps of: (a) dilating said vascular circulation system by introducing adenosine or an adenosine agonist into said vascular circulation system in order to increase the flow of blood into said region; (b) introducing a blood flow marking medium into said region; (c) reducing the amount of adenosine or said adenosine agonist necessary to dilate the vascular circulation system by introducing an A **adenosine receptor antagonist** into said vascular circulatory system; and (d) determining the amount of marking medium in said region.

12. The method of claim 11 wherein the A_1 **adenosine receptor** agonist is ##STR5## wherein R^1 is hydrogen or R_2 ; R_2 is selected from the group consisting of endo-2-norbornyl or cyclopentyl; R_3 is selected from the group consisting of hydrogen, halogen, amine, carboxy, alkyl radicals having 1 to 10 carbon atoms, cycloalkyl radicals having from 3 to 8, preferably 5 to 6, ring carbon atoms, thio, sulfonate, sulfonamide, sulfon, sulfoxamide, phenyl, alkyl-substituted amine, and cycloalkyl substituted amine; R_4 is selected from the group consisting of benzyl, phenyl, and alkyl groups comprising from 1 to 4 carbon atoms, wherein said alkyl group can be substituted with oxygen, for instance ethers and alcohols; and R_5 is selected from the group consisting of hydrogen; hydroxy; sulfonate; halogen; alkoxy and cycloalkoxy groups comprising 1 to 6 carbon atoms.

13. The method of claim 11 wherein the A_1 **adenosine receptor** agonist is an N^6 -norbornyl substituted adenine.

14. The method of claim 31 wherein the A_1 **adenosine receptor** agonist is selected from the group consisting of: N^6 -(endo-2-norbornyl)-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-bromo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-amino-9-methyl adenine, N^6 -(endo-2-norbornyl)-9-[(2-hydroxyethoxy)methyl]adenine, N^6 -(endo-2-norbornyl)-8-thio-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-chloro-9-methyl adenine, N^6 -(endo-2-norbornyl)-2-oxo-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-amine-9-methyl adenine, N^6 -(endo-2-norbornyl)-8-cyclopentyl-9-methyl adenine, and N^6 -(exo-2-norbornyl)-9-methyl adenine.

15. The method of claim 11 wherein the A_1 **adenosine receptor** agonist is selected from the group consisting of N^6 -3-pentyl-9-methyl adenine, N^6 -cyclopentyl-9-methyl adenine, N^6 -1-(2-thienyl)-2-butyl-methyl adenine, and N^6 -cyclopentyl-8-cyclopentyl-9-methyl adenine.

16. The method of claim 11 wherein said marking medium is selected from the group consisting of thallium-201 and rubidium-82.

17. The method of claim 16 wherein said marking medium comprises thallium-201.

18. The method of claim 17 wherein adenosine is introduced into said vascular circulatory system.

19. The method of claim 18 wherein the amount of marking medium in said region is determined by non-invasive myocardial imaging of the blood flow to said region.

20. The method of claim 19 wherein said N^6 -norbornyl substituted adenine is N^6-(endo-norbornyl)-9-methyl adenine.

21. In a method for determining the viability of tissue in a region of an organism having a vascular circulatory system that supplies blood to said region the improvement which comprises the steps of; (a) dilating said vascular circulation system by introducing adenosine or an adenosine agonist into said vascular circulation system in order to increase the flow of blood into said region; and, (b) alleviating the non-dilating effects of adenosine or said adenosine agonist by introducing an A1 **adenosine receptor antagonist** into said vascular circulatory system.

L14 ANSWER 56 OF 56 USPATFULL on STN
88:57298 **Adenosine receptor antagonists.**
Snyder, Solomon H., Baltimore, MD, United States
Daly, John W., Bethesda, MD, United States
Bruns, Robert F., Ann Arbor, MI, United States
The Johns Hopkins University, Baltimore, MD, United States (U.S. corporation)
US 4769377 19880906
APPLICATION: US 1986-825594 19860203 (6)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound of the formula ##STR4## or the pharmaceutically-acceptable salts, esters, amides, glycosides or formaldehyde complexes thereof, wherein: X is NH; R_1 is allyl or alkyl of 3 carbons; R_2 is allyl, or alkyl of 3 carbons; R_3 is H, NH_2 or OH; R_4 is phenyl, hydroxy or cycloalkoxy; and R_5, which may be the same or different, are hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, nitro or amino.

2. The compound 8-(2-amino-4-chlorophenyl)theophylline.

3. In a method involving **adenosine receptor** blocking by administering an **adenosine receptor antagonist**, the improvement which comprises using, as the **antagonist**, a compound according to claim 1.

=> d l14,cbib,clm,20-39

L14 ANSWER 20 OF 56 USPATFULL on STN
2002:141535 Compositions and methods for the treatment of anorectal disorders.
Parks, Thomas P., San Mateo, CA, UNITED STATES
Mak, Vivien, Palo Alto, CA, UNITED STATES
Lee, Jung-Chung, Sunnyvale, CA, UNITED STATES
Lee, Charles, Union City, CA, UNITED STATES
US 2002072522 A1 20020613
APPLICATION: US 2001-919590 A1 20010730 (9)
PRIORITY: US 2000-222267P 20000731 (60)
US 1998-112325P 19981214 (60)
US 1999-139916P 19990617 (60)
US 1999-155318P 19990921 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition for the treatment of an anorectal disorder, and for controlling the pain associated therewith, said composition comprising at least one internal anal sphincter relaxing agent selected from the group consisting of NO donors, phosphodiesterase type II inhibitors,

phosphodiesterase type IV inhibitors, phosphodiesterase type V inhibitors, nonspecific phosphodiesterase inhibitors, superoxide scavengers, β-adrenergic agonists, cAMP-dependent protein kinase activators, $\alpha_{1\text{-adrenergic}}$ **antagonists**, estrogens, ATP-sensitive K+ channel activators, **adenosine receptor antagonists**, and smooth muscle relaxants, with a pharmaceutically acceptable carrier.

2. A composition in accordance with claim 1, wherein said composition comprises a first agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1, and a second agent that is an adrenergic receptor **antagonist**.

3. A composition in accordance with claim 1, wherein said carrier is formulated for local application.

4. A composition according to claim 1, wherein said composition comprises a first relaxing agent that is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1 and a second agent that is a $\beta_{2\text{-adrenergic}}$ agonist.

5. A composition according to claim 4, wherein said β_2-adrenergic agonist is salbutamol or terbutaline.

6. A composition in accordance with claim 1, wherein said composition comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1 and a second agent that is an ATP sensitive K+ channel activator.

7. A composition in accordance with claim 6, wherein said second agent is minoxidil or diazoxide.

8. A composition in accordance with claim 1, wherein said composition comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1 and a second agent that is an **adenosine receptor antagonist**.

9. A composition in accordance with claim 8, wherein said second agent is theophylline or dyphylline.

10. A composition according to claim 1, comprising an **adenosine receptor antagonist**.

11. A composition according to claim 10, wherein said **antagonist** is theophylline or dyphylline.

12. A composition according to claim 1, comprising a ATP sensitive K+ channel opener.

13. A composition according to claim 12, wherein said opener is minoxidil or diazoxide.

14. A composition according to claim 1, wherein said composition comprises a $\beta_{2\text{-adrenergic}}$ agonist.

15. A composition according to claim 14, wherein said $\beta_{2\text{-adrenergic}}$ agonist is salbutamol or terbutaline.

16. A method of treating an anorectal disorder, and for controlling the pain associated therewith, the method comprising administering to a subject in need of such treatment a therapeutically effective amount of a composition that comprises at least one internal anal sphincter relaxing agent selected from the group consisting of NO donors, phosphodiesterase type II inhibitors, phosphodiesterase type IV inhibitors, phosphodiesterase type V inhibitors, nonspecific phosphodiesterase inhibitors, superoxide scavengers, β-adrenergic agonists, cAMP-dependent protein kinase activators, α_1-adrenergic **antagonists**, estrogens, L-type Ca^{2+} channel blockers, ATP-sensitive K+ channel activators, **adenosine receptor antagonists** and smooth muscle relaxants.

17. A method in accordance with claim 16, wherein said composition comprises a first agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1, and a second agent that is an adrenergic receptor **antagonist**.

18. A method in accordance with claim 16, wherein said administering is by local application.

19. A method according to claim 16, wherein said composition comprises a first relaxing agent that is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1 and a second agent that is a $\beta_{2\text{-adrenergic}}$ agonist.

20. A method according to claim 19, wherein said $\beta_{2\text{-adrenergic}}$ agonist is salbutamol or terbutaline.

21. A method in accordance with claim 16, wherein said composition comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1 and a second agent that is an ATP sensitive K+ channel activator.

22. A method in accordance with claim 21, wherein said second agent is minoxidil or diazoxide.

23. A method in accordance with claim 16, wherein said composition comprises a first relaxing agent which is a NO donor selected from the group consisting of nitroglycerin, L-arginine, SNAP, GSNO and SIN-1 and a second agent that is an **adenosine receptor antagonist**.

24. A method in accordance with claim 23, wherein said second agent is theophylline or dyphylline.

25. A method according to claim 16, wherein said composition comprises an **adenosine receptor antagonist**.

26. A method according to claim 25, wherein said **antagonist** is theophylline or dyphylline.

27. A method according to claim 16, wherein said composition comprises a ATP sensitive K+ channel opener.

28. A method according to claim 28, wherein said activator is minoxidil or diazoxide.

29. A method according to claim 16, wherein said composition comprises a $\beta_{2\text{-adrenergic}}$ agonist.

30. A method according to claim 29, wherein said $\beta_{2\text{-adrenergic}}$ agonist is salbutamol or terbutaline.

31. A method in accordance with claim 16, wherein said anorectal disorder is an anal fissure.

32. A method of claim 16, wherein said composition comprises a terbutaline or salbutamol.

33. A method of claim 16, wherein said composition comprises theophylline or diphylline.

34. A method of claim 16, wherein said composition comprises minoxidil or diazoxide.

L14 ANSWER 21 OF 56 USPATFULL on STN
2002:119616 Method of identifying ligands of biological target molecules.
Elling, Christian E., Copenhagen, DENMARK
Holst Lange, Birgitte, Copenhagen, DENMARK
Schwartz, Thue W., Frederiksburg, DENMARK
Gerlach, Lars Ole, Copenhagen, DENMARK
Pedersen, Jan Torleif, Bronshoj, DENMARK
US 2002061599 A1 20020523
APPLICATION: US 2000-752102 A1 20001229 (9)
PRIORITY: DK 1999-1879 19991230
DK 1999-1880 19991230
DK 2000-705 20000428
US 2000-175664P 20000112 (60)
US 2000-175401P 20000111 (60)
US 2000-202990P 20000509 (60)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A drug discovery process for identification of a small organic compound that is able to bind to a biological target molecule, the process comprising mutating a biological target molecule in such a way that at least one amino acid residue capable of binding a metal ion is introduced into the biological target molecule so as to obtain a metal ion binding site as an anchor point in the mutated biological target molecule.

2. A drug discovery process according to claim 1 further comprising (a) contacting the mutated biological target molecule with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the introduced metal ion binding site of the mutated biological target molecule, and (b) detecting any change in the activity of the mutated biological target molecule or determining the binding affinity of the test compound to the mutated biological target molecule.

3. A drug discovery process according to claim 1 further comprising (a) contacting the mutated biological target molecule with one or more members of a library of test compounds that comprise a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of at least a member of the library of test compounds to the introduced metal ion binding site of the mutated biological target molecule, and (b) detecting any change in the activity of the mutated biological target molecule or determining the binding affinity of the test compound to the mutated biological target molecule.

4. A drug discovery process for identification of a small organic compound that is able to bind to a biological target molecule which has at least one metal ion binding site, the process comprising (a) contacting the biological target molecule with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the metal ion binding site of the biological target molecule, and (b) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

5. A drug discovery process for identification of a small organic compound that is able to bind to a biological target molecule which bas at least one metal ion binding site, the process comprising (a) contacting the biological target molecule with one or more members of a library of test compounds that comprise a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of at least a member of the library of test compounds to the metal ion binding site of the biological target molecule, and (b) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

6. A drug discovery process according to any of claims 1-5 further comprising (c) identifying the test compound that non-covalently binds to the biological target molecule.

7. A drug discovery process according to any of claims 1-6 further comprising (d) selecting two or more test compounds capable of forming a non-covalent binding to a biological target molecule, and capable of changing the activity of the biological target molecule or the binding affinity of the test compound to the biological target molecule to form a library of test compounds.

8. A drug discovery process according to any of claims 1-3 or 6-7 further comprising (e) contacting the biological target molecule in wild-type, non-mutated form with at least one test compound determined to non-covalently bind the mutated biological target molecule in step (a), and (f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target moelcule.

9. A drug discovery process according to any of claims 1-3 or 6-7 further comprising (e) contacting the biological target molecule in

wild-type, non-mutated form with two or more members of a library of test compounds, wherein the test compounds in chelated form have been determined to non-covalently bind the mutated biological target molecule in step (a), and (f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target moelcule.

10. A drug discovery process according to claims 8 or 9 further comprising (g) identifying the test compound that interacts with the wild-type biological target molecule.

11. A drug discovery process according to any of claims 1-7 further comprising (e) contacting the biological target molecule in wild-type, non-mutated form with at least one test compound determined to non-covalently bind the mutated or non-mutated biological target molecule in step (a) but lacking a metal ion chelated thereto, and (f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the non-chelated test compound to the biological target moelcule.

12. A drug discovery process according to any of claims 1-7 further comprising (e) contacting the biological target molecule in wild-type, non-mutated form with two or more members of a library of non-chelated test compounds, wherein the test compounds in chelated form have been determined to non-covalently bind the mutated or non-mutated biological target molecule in step (a), and (f) detecting any change in the activity of the biological target molecule or determining the binding affinity of the non-chelated test compound to the biological target moelcule.

13. A drug discovery process according to claims 11 or 12 further comprising (g) identifying the non-chelated test compound that interacts with the wild-type biological target molecule.

14. A drug discovery process according to any of claims 8-13 further comprising (a) identification of any binding or interaction between the non-chelated test compound and the wild-type biological target molecule.

15. A drug discovery process according to any of claims 1-14, wherein the biological target molecule is a protein.

16. A drug discovery process according to claims 15, wherein the protein comprises an amino acid residue and wherein the metal ion binding site in the protein is introduced by amino acid substitution at or in the vicinity of 1) a site where the binding of the test compound will interfere with the binding to another protein, for example a regulatory protein, or to a domain of the same protein; 2) a site where the binding of the test compound will interfere with the cellular targeting of the protein; 3) a site where the binding of the test compound will directly or indirectly interfere with the binding of substrate or the binding of an allosteric modulatory factor for the protein; 4) a site where the binding of the test compound may interfere with the intra-molecular interaction of domains within the protein, for example the interaction of a regulatory domain with a catalytic domain; 5) a site where binding of the test compound will interfere with the folding of the protein, for example the folding of the protein into its active conformation; or 6) a site where the binding of the test compound will control the activity of the protein, for example by an allosteric mechanism.

17. A drug discovery process according to any of the preceding claims, wherein the metal ion binding amino acid residue in the biological target molecule is introduced by site-directed mutagenesis.

18. A drug discovery process according to any of the preceding claims, wherein the mutated biological target molecule is obtained as a recombinant expression product in purified or non-purified form.

19. A drug discovery process according to any of the preceding claims, wherein the mutated biological target molecule is obtained as a synthetic or semi-synthetic product.

20. A drug discovery process according to claim 15, wherein step (a) in any of claims 2-5 comprises the further step of determining, based on the three-dimensional stucture of the specific protein in question or

the primary structure of the specific protein together with a three-dimensional model of the class of proteins to which the specific protein belongs, the location of the metal ion binding amino acid residue in the mutated or non-mutated protein, and determining the location of at least one other amino acid residue in the vicinity of the metal ion binding amino acid residue.

21. A drug discovery process according to claim 15, wherein the binding of the test compound to the mutated or non-mutated protein in step (a) in any of claims 2-5 is determined using detection of any changes in the biological activity of the protein, competition with binding of a labelled ligand of the protein, or using a metal ion chelator which is in itself detectable or labelled with a detectable labelling agent.

22. A drug discovery process according to claim 19, wherein the amino acid residue in the vicinity of the metal ion binding amino acid residue is one which is capable of directly or indirectly binding at least one functional group of the test compound other than the metal ion.

23. A drug discovery process according to claim 22, wherein the amino acid residue capable of binding at least one functional group of the test compound other than the metal ion is detected using site-directed mutagenesis of at least one amino acid residue of the protein potentially involved in interaction with said functional group of the test compound other than the metal ion, followed by expression of the mutated protein in a suitable cell, contacting said cell or a portion thereof including the mutated protein with the test compound, and detecting any changes in the activity of the protein, determining any effect on binding in a competitive binding assay using a labelled ligand of the protein, or using a chelating agent which is in itself detectable or labelled with a detectable labelling agent.

24. A drug discovery process according to claim 22, wherein the amino acid residue capable of binding at least one functional group of the test compound other than the metal ion is detected by structural analysis employing i) a process involving crystallisation followed by X-ray, or ii) a process involving NMR.

25. A drug discovery process according to claim 15, wherein step (a) of any claims 2-5 comprises the further steps of improving the binding affinity of a metal ion chelate to the mutated or non-mutated protein, the method comprising (i) selecting a metal ion chelate with an activity to or a binding affinity to the mutated protein of 50 μM or better as identified by the method of claim 21, (ii) mapping the site of the protein to which the chelate binds using the method of claim 20, 23 and/or 24, (iii) optionally locating at least one amino acid residue in the vicinity of the chelate, (iv) altering one or more functional group of the chelate to optimise for direct or indirect interaction with said amino acid residue to generate a library of chelate derivatives, (v) screening the derivatives of step (iv) by the method of claim 21, (vi) selecting metal ion chelates having at least a two fold increase in activity or in binding affinity, (vii) optionally repeating any one or a combination of two or more of steps (i)-(vi) one or more times to generate metal ion chelating compounds with an improved binding affinity for the mutated or non-mutated protein, and (viii) optionally screening the thus selected metal ion chelates for binding to the wild-type protein by the method of claim 21, (ix) optionally selecting metal ion chelates having at least an activity or a binding affinity to the wild-type protein of 50 μM or better as identified by the method of claim 21, and (x) optionally repeating any one or a combination of two or more of steps (viii)-(ix) one or more times to generate metal ion chelating compounds with an improved binding affinity for the wild-type protein.

26. A drug discovery process according to claim 15, wherein step (e) in any of claims 8-12 comprises the further steps of generating a library of test compounds which are derivatives of a test compound found to interact with the wild-type protein in step (e), each test compound in the library being provided with at least one functional group for direct or indirect interaction with at least one amino acid of the wild-type protein, which functional group differs from at least one functional group of each of the other test compounds, and screening the test compound library for compounds interacting with the wild-type protein.

27. A drug discovery process according to claim 15, wherein step (e) in

any of claims 8-12 is performed by detecting any changes in the activity of the protein, detecting an effect on binding in a competitive binding assay using a labelled ligand of the protein, or using a chelating agent which is in itself detectable or labelled with a detectable labelling agent.

28. A drug discovery process according to claim 15, wherein step (e) in any of claims 8-12 comprises the further step of determining--based on the three-dimensional structure of the specific protein in question or the primary structure of the specific protein together with the three-dimensional model of the class of proteins to which the specific protein belongs, and based on the information provided by the method of claim 25 of the location of amino acid residues in the vicinity of the metal ion binding residue introduced in the mutated protein--the location of an amino acid residue in the wild-type protein binding at least one functional group of a test compound.

29. A drug discovery process according to claim 28 wherein the amino acid residue capable of binding at least one functional group of the test compound is detected using site-directed mutagenesis of at least one amino acid residue of the wild-type protein potentially involved in interaction with said functional group of the test compound, followed by expression of the mutated protein in a suitable cell, contacting said cell or a portion thereof including the mutated protein with the test compound, and determining any effect on binding using detection of any changes in the biological activity of the protein, a competitive binding assay using a labelled ligand of the protein, or using a chelating agent which is in itself detectable or labelled with a detectable labelling agent.

30. A drug discovery process according to claim 28, wherein the amino acid residue capable of binding at least one functional group of the test compound other than the metal ion is detected by structural analysis employing i) a process involving crystallisation followed by X-ray, or ii) a process involving NMR.

31. A drug discovery process according to any of claims 1-14, wherein the biological target molecule is selected from the group consisting of proteins, polypeptides, oligopeptides, nucleic acids, carbohydrated, nucleoproteins, glycoproteins, glycolipids, lipoproteins and derivatives thereof.

32. A drug discovery process according to claim 31, wherein the biological target molecule is a protein selected from the group consisting of membrane receptors, signal transduction proteins, scaffolding proteins, nuclear receptors, steroid receptors, intracellular receptors, transcription factors, enzymes, allosteric enzyme regulator proteins, growth factors, hormones, neuropeptides or immunoglobulins.

33. A drug discovery process according to claim 32, wherein the protein is a membrane protein.

34. A drug discovery process according to claim 33, wherein the biological target molecule is a membrane protein and the metal ion binding site in the biological target molecule is introduced in a ligand binding crevice of the membrane protein.

35. A drug discovery process according to claim 33, wherein the membrane protein is an integral membrane protein.

36. A drug discovery process according to claim 35, wherein the membrane protein comprises 1-14 transmembrane domains such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 domains.

37. A drug discovery process according to claim 36, wherein the membrane protein is a receptor such as a tyrosine kinase receptor, e.g. a growth factor receptor such as the growth hormone, insulin, epidermal growth factor, transforming growth factor, erythropoietin, colony-stimulating factor, platelet-derived growth factor receptor or nerve growth factor receptor (TrkA or TrkB).

38. A drug discovery process according to claim 36, wherein the membrane protein is a purinergic ion channel.

39. A drug discovery process according to claim 36, wherein the membrane protein is a ligand-gated ion channel, such as a nicotinic acetylcholine receptor, GABA receptor, or glutamate receptor (NMDA or AMPA).

40. A drug discovery process according to claim 36, wherein the membrane protein is a voltage-gated ion channel, such as a potassium, sodium, chloride or calcium channel.

41. A drug discovery process according to claim 36, wherein the membrane protein is a 7TM receptor, a G-protein coupled receptor, such as the acetylcholine receptors, ACTH receptors, **adenosine receptors**, adrenoceptors, anaphylatoxin chemotactic receptor, angiotensin receptors, bombesin (neuromedin) receptors, bradykinin receptors, calcitonin and calcitonin gene related peptide receptors, conopressin receptors, corticotropin releasing factor receptors, amylin receptors, adrenomedullin receptors, calcium sensors, cannabinoid receptors, CC-chemokine receptors, cholecystokinin receptors, dopamine receptors, eicosanoid receptors, endothelin receptors, fMLP receptors, $GABA_B$ receptors, galanin receptors, gastrin receptors, gastric inhibitory peptide receptors, glucagons receptors, gluragon-like I and II receptors, glutamate metabotropic receptors, glycoprotein hormone (e.g. FSH, LSH, TSH, LH) receptors, gonaotopin releasing hormone receptors, growth hormone releasing hormone receptors, growth hormone releasing peptide (Ghrelin) receptors, histamine receptors, 5-hydroxytryptamine receptors, leukotriene receptors, lysophospholipid receptors, melanocortin receptors, melanin concentrating hormone receptors, melatonin receptors, melanocortin receptors, neuropeptide Y receptors, neurotensin receptors, odor component receptors, opioid and opioid-like receptors, retinal receptors (opsins), orexin receptors, oxytocin receptors, parathyroid hormone and parathyroid hormone-related peptide receptors, P2Y receptors, pheromone receptors, platelet-activating factor receptors, prostanoid receptors, protease-activated receptors, secretin receptors, somatostatin receptors, tachykinin receptors, thyrotropin-releasing hormone receptors, pituitary adenylate activating peptide receptors, vasopressin receptors, vasoactive intestinal peptide receptors and virally encoded 7TM receptors; in particular galanin receptors, P2Y receptors, chemokine receptors, metabotropic glutamate receptors, melanocortin receptors, bombesin receptors, cannabinoid receptors, lysophospholipid receptors, fMLP receptors, neuropeptide Y receptors, tachykinin receptors, dopamine receptors, histamine receptors, 5-hydroxytryptamine receptors, histamine receptors, mas-proto-oncogene, acetylcholine, oxytocin, herpes virus encoded 7TM receptors, epstein-barr virus induced 7TM receptors, cytomegalovirus encoded receptors and bradykinin receptors; preferably galanin receptor type 1, leukotiene B4 receptor, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CX3CR1, mGLU-R1, mGLU-R2, m-GLU-F3, m-GLU-R4, m-GLU-R5, m-GLU-R6, m-GLU-R8, melanin concentration hormone receptors, melanocortin-1 receptor, melanocortin-3 receptor, melanocortin-4 receptor, melanocortin-5 receptor, bombesin receptor subtype 3, cannabinoid receptor 1, cannabinoid receptor 2, EDG-2, EDG-4, FMLP-related receptor I, FMLP-related receptor II, NPY Y6 receptor, NPY Y5 receptor, NPY Y4 receptor, NK-1 receptor, NK-3 receptor, D2 receptor (short), D2 receptor (long), Duffy antigen, U27, U28, UL33 and U78 from human cytomegalovims, U12 and, U51 from human herpes virus 6A, 6B or 7, ORF-74 from human herpes virus 8, Epstein Barr virus induced receptor-2, histamine H1 receptor, MAS proto-oncogene, muscarinic M1 receptor, muscarinic M2 receptor, muscarinic M3 receptor, muscarinic M5 receptor, oxytocin receptor, XCR1 receptor, RDC1 receptor, GPR12 receptor or GPR3 receptor.

42. A drug discovery process according to claim 36, wherein the membrane protein is a transporter protein, such as a GABA, monoamine, glutaminic acid or nucleoside transporter.

43. A drug discovery process according to claim 36, wherein the membrane protein is a multidrug resistance protein, e.g. a P-glycoprotein, multidrug resistance associated protein, drug resistance associated protein lung resistance related protein breast cancer resistance protein, adenosine triphosphate-binding cassette protein Byr, QacA or EmrAB/TolC pump.

44. A drug discovery process according to claim 36, wherein the membrane protein is a cell adhesion molecule, e.g. NCAM, VCAM or ICAM.

45. A drug discovery process according to claim 36, wherein the membrane

protein is an enzyme such as adenylyl cyclase.

46. A drug discovery process according to claim 35, wherein the membrane protein is an orphan receptor.

47. A method of identifying a metal ion binding site in a biological target molecule, the method comprising (a) contacting the biological target molecule with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the biological target molecule, and (b) detecting any change in the activity of the biological target molecule or determining the binding affinity of the test compound to the biological target molecule.

48. A method of identifying a metal ion binding site in a protein, the method comprising (a) analysing the nucleotide sequence of the gene coding for the protein in order to deduce the amino acid sequence, (b) building a molecular model of the protein or a part of the protein based on the deduced amino acid sequence and the generic three-dimensional model of the class of proteins to which the specific protein belongs, (c) identifying the presence of amino acid residues such as, e.g., histidine, cysteine and/or aspartate residues, capable of binding a metal ion and located in suitable relative positions.

49. A method according to claim 47 or 48, wherein the test compound is contacted with two or more biological target molecules for identification of possible metal ion binding sites thereof.

50. A method of identifying a metal ion binding site in a protein, the method comprising (a) selecting a nucleotide sequence suspected of coding for a protein and deducing the amino acid sequence thereof, (b) expressing said nucleotide sequence in a suitable host cell, (c) contacting said cell or a portion thereof including the expressed protein with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the protein, and detecting any change in the activity of the protein or determining the binding affinity of the test compound to the protein, and (d) determining, based on the generic three-dimensional model of the class of proteins to which the protein or suspected protein belongs, at least one metal ion binding amino acid residue located in said protein to locate the metal ion binding site of said protein.

51. A method of mapping a metal ion binding site of a protein, the method comprising (a) contacting the protein with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the protein, and detecting any change in the activity of the protein or determining the binding affinity of the test compound to the protein, and (b) determining, based on the primary structure of the specific protein in question and the generic three-dimensional model of the class of proteins to which the specific protein of step (a) belongs, at least one metal ion binding amino acid residue located in the membrane protein to identify the metal ion binding site of said membrane protein.

52. A drug discovery process according to any of claims 1-46 further comprising a method of any of claims 47-51.

53. A drug discovery process according to any of the preceding claims, wherein the test compound has a log K value in a range of from about 3 to about 18 such as, e.g. from about 3 to about 15, from about 3 to about 12, from about 4 to about 10, from about 4 to about 8, from about 4.5 to about 7, from about 5 to about 6.5 such as from about 5.5 to about 6.5.

54. A drug discovery process according to any of the preceding claims, wherein the test compound forms a chelate with a metal ion selected from the group consisting of Co, Cu, Ni, Pt and Zn including the various oxidation steps such as, e.g., Co (II), Co (III), Cu (I), Cu (II), Ni (II), Ni (III), Pt (II), Pt (IV) and Zn (II).

55. A drug discovery process according to any of the preceding claims, wherein the test compound has at least two heteroatoms, similar or different, selected from the group consisting of nitrogen (N), oxygen

(O), sulfur (S), selenium (Se) and phosphorous (P).

56. A drug discovery process according to any of the preceding claims, wherein the test compound has the general formula I ##STR58## wherein F is N, O, S, Se or P; and G is N, O, S, Se or P; at least one of $(X)_n$ and $(Y)_m$ is present and if n is 0, then $--(X)_{n}--$ is absent, and if m is 0; then $--(Y)_{m}--$ is absent, and both n and m are not 0; R^1 and R^2, which are the same or different, are radicals preferably selected from the group consisting of hydrogen, a C_{1-C15} alkyl, C_{2-C15} alkenyl, C_{2-C15} alkynyl, aryl, cycloallyl, alkoxy, ester, --OCOR', --COOR', heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl group, an amine, imine, nitro, cyano, hydroxyl, alkoxy, ketone, aldelhyde, carboxylic acid, thiol, amide, sulfonate, sulfonic acid, sulfonamide, phosphonate, phosphonic acid group or a combination thereof, optionally substituted with one or more substituents selected from the same group as R^1 and/or a halogen such as F, Cl, Br or I; R' is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkenyl, substituted heteroalkenyl, heteroalkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocycloalkyl, substituted heterocycloalkyl, heterocycloalkenyl or substituted heterocycloalkenyl; R^1 and/or R^2 optionally forming a fused ring together with any of F, $(X)_n$ or a part of $(X)_n$ G, $(Y)_m$ or a part of $(Y)_m$ or R^1 and R^2 themselves forming a fused ring; X and Y are the same or different and have the same meaning as R' such as, e.g., $--CH_{2}--$, $--CH_{2}--CH2--$, $--CH_{2}--S--CH2--$, $--CH_{2}--N--CH_{2}--$, --CH.dbd.CH--CH.dbd.CH--, $--(CH_2)_{d}--(Z)_{e}(V)_{f}--(W)_{g}--(CH_2)_{h}--$, $--CH_{2}--O--CH_{2}--$, wherein each of Z and W are independently C, S, O, N, Se or P and V is --CH-- or $--CH_{2}--$; $(X)_n$ and/or $(Y)_m$ optionally being substituted with one or more substituents selected from the same group as R^1 and/or a halogen such as F, Cl, Br or I; n is 0 or an integer of 1-5, m is 0 or an integer of 1-5, e and/or g are an integer of 1-3, d, f and/or h are an integer of 1-7.

57. A drug discovery process according to claim 56, wherein the test compound has the general formula II ##STR59## wherein F, G, R^1 and R^2 have the same meaning as in claim 56, R^3 and R^4 have the same meaning as R^1 and/or R^2, and A and B have independently the same meaning as X and Y in formula I, n and m have the same meaning as in formula I except that n and m may be 0 at the same time and then the basic structure is $R^{1}--F--G--R^{2}$ and when n or m are 0, respectively, then the basic structures of formula II are ##STR60##

58. A drug discovery process according to claim 57, wherein F and/or G is nitrogen (N) and/or oxygen (O) and the test compound has the general formula III, IV, V, VI or VII: ##STR61## wherein T and Q are heteroatoms, and q and s independently are 0 or an integer of from 1 to 4; the meanings of q and s for q and/or s being 0 are the same as in Formula II for n and m; a circle indicates a fused alkyl, alkenyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl or heteroaryl ring having from 3-7 atoms in the ring; R^5 has the same meaning as R^1 and/or R^2; and in Formulas III C-G, IV C and V C-D, T and/or Q may be placed anywhere in the cyclic system.

59. A drug discovery process according to claim 58, wherein the test compound has the general formula VIII ##STR62## wherein R^3, R^4, Z, W and P are as defined herein before, a and/or b are an integer of 1-7 and c is 0 or an integer of 1-7, and each of Q and T is independently --CH-- or $--CH_{2}--$, s is an integer of 1-7, and t is an integer of 1-7, are believed to be particularly suitable; when c is 0 in the above Formula VIII then $--(P)_{c}--$ is absent, i.e. there is no bond between $(Z)_a$ and $(W)_b$.

60. A drug discovery process according to claim 56, wherein the test compound as the general formula IX ##STR63## wherein R^3, R^4, P, X and n are as indicated above, and r is 0 or an inter of 1-3, and when r is 0 then $--(P)_{r}--$ is absent.

61. A drug discovery process according to claim 56, wherein the test compound has the general formula X ##STR64## wherein F is N, O or S and G is N, O or S, n is an integer from 1 to 5, m is 0 or an integer from 1 to 5, p and/or r are 0 or an integer from 1 to 8, u is an integer from 1 to 8, and R has the same meaning as R^1 in Formula I.

62. A drug discovery process according to claim 56, wherein the test compound has the general formula XI ##STR65## wherein R^3 and R^4 are as indicated above in formula I.

63. A drug discovery process according to any of claims 53-62, wherein the metal ion is one that binds to an amino acid residue containing a S, O, N, Se and/or P atom or with an aromatic amino acid residue.

64. A drug discovery process according to claim 63, wherein the amino acid residue is selected from the group consisting of Ser, Lys, Arg, Tyr, Thr, Trp, Phe, Asp, Glu, Asn, Gin, Cys and His, in particular Asp, Glu, Cys and His, preferably His.

65. A drug discovery process according to any of claims 53-64, wherein the metal ion is selected from the group consisting of aluminium, antimony, arsenic, astatine, barium, beryllium, bismuth, boron, cadmium, calcium, cerium, cesium, chromium, cobalt, copper, dysprosium, erbium, europium, gadolinium, gallium, germanium, gold, hafnium, holmium, indium, iridium, iron, lanthanum, lead, lutetium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, osmium, palladium, platinum, polonium, praseodymium, promethium, rhenium, rhodium, rubidium, ruthenium, samarium, scandium, selenium, silicon, silver, strontium, tantalum, technetium, tellurium, terbium, thallium, thorium, thulium, tin, titanium, tungsten, vanadium, ytterbium, yttrium, zinc, zirconium, and oxidation states and isotopes thereof, in particular aluminium, antimony, barium, bismuth, calcium, chromium, cobalt, copper, europium, gadolinium, gallium, germanium, gold, indium, iron, lutetium, manganese, magnesium, nickel, osmium, palladium, platinum, rhenium, rhodium, rubidium, ruthenium, samarium, silver, strontium, technetium, terbium, thallium, thorium, tin, yttrium, zinc, and oxidation states or isotopes thereof; in particular cobalt, copper, nickel, platinum, ruthenium, and zink, and oxidation states and isotopes thereof, preferably calcium (II), cobalt (II) and (III), copper (I) and (II), europium (III), iron (II) and (III), magnesium (II), manganese (II), nickel (II) and (III), palladium (II), platinum (II) and (V), ruthenium (II), (III), (IV), (VI) and (VIII), samarium (III), terbium (III), zinc (II), or isotopes thereof, preferably cobalt (II) and (III), copper (I) and (II), nickel (II) and (III), zinc (II) and platinum (II) and (V), or isotopes thereof.

66. A drug discovery process according to any of claims 53-65, wherein the test compound is a chelate like e.g. metal ion-phenanthroline complex, metal ion bipyridyl complex and metal ion-1,4,8,11-tetraazacyclotetradecane complex such as, e.g., a Cu^{2+}-phenanthroline complex, a Zn^{2+}-phenanthroline complex, a Cu^{2+}-bipyridyl complex, a Zn^{2+}-bipyridyl complex, a Ca^{2+}-bipyridyl complex, a Cu^{2+}-1,4,8,11-tetraacyclotetradecane, a Zn^{2+}-1,4,8,11-tetraazacyclotetradecane.

67. A chemical library comprising a plurality of test compounds of the following general formula I ##STR66## wherein F is N, O, S, Se or P; and G is N, O, S, Se or P; at least one of $(X)_n$ and $(Y)_m$ is present and if n is 0, then $--(X)_n--$ is absent, and if m is 0, then $--(Y)_m--$ is absent, and both n and m are not 0; R^1 and R^2, which are the same or different, are radicals preferably selected from the group consisting of: hydrogen, a C_{1-C15} alkyl, C_{2-C15} alkenyl, C_{2-C15} alkynyl, aryl, cycloalkyl, alkoxy, ester, --OCOR', --COOR', heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl group, an amine, imine, nitro, cyano, hydroxyl, alkoxy, ketone, aldelhyde, carboxylic acid, thiol, amide, sulfonate, sulfonic acid, sulfonamide, phosphonate, phosphonic acid group or a combination thereof, optionally substituted with one or more substituents selected from the same group as R^1 and/or a halogen such as F, Cl, Br or I; R' is hydrogen, alkyl, substituted allyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkenyl, substituted heteroalkenyl, heteroalkynyl, heteroaryl,

substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocycloalkyl, substituted heterocycloalkyl, heterocycloalkenyl or substituted heterocycloalkenyl; R^1 and/or R^2 optionally forming a fused ring together with any of F, $(X)_n$ or a part of $(X)_n$ G, $(Y)_m$ or a part of $(Y)_m$ or R^1 and R^2 themselves forming a fused ring; X and Y are the same or different and have the same meaning as R' such as, e.g. $--CH_2--$, $--CH_2--CH2--$, $--CH_2--S--CH2--$, $--CH_2--NCH2--$, --CH.dbd.CH--CH.dbd.H--, $--(CH_2)_d--(Z)_e--(V)_f--(W)_g--(CH_2)_h--$, $--CH_2--O--CH2--$, wherein each of Z and W are independently C, S, O, N, Se or P and V is --CH-- or $--CH_2--$; $(X)_n$ and/or $(Y)_m$ optionally being substituted with one or more substituents selected from the same group as R^1 and/or a halogen such as F, Cl, Br or I; n is 0 or an integer of 1-5, m is 0 or an integer of 1-5, e and/or g are an integer of 1-3, d, f and/or h are an integer of 1-7, the test compounds being in the form of chelates formed between the test compound and a metal ion or atom selected from the group consisting of aluminium, antimony, arsenic, astatine, barium, beryllium, bismuth, boron, cadmium, calcium, cerium, cesium, chromium, cobalt, copper, dysprosium, erbium, europium, gadolinium, gallium, germanium, gold, hafnium, holmium, indium, indium, iron, lanthanum, lead, lutetium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, osmium, palladium, platinum, polonium, praseodymium, promethium, rhenium, rhodium, rubidium, ruthenium, samarium, scandium, selenium, silicon, silver, strontium, tantalum, technetium, tellurium, terbium, thallium, thorium, thulium, tin, titanium, tungsten, vanadium, ytterbium, yttrium, zinc, zirconium, and oxidation states and isotopes thereof; in particular aluminium, antimony, barium, bismuth, calcium, chromium, cobalt, copper, europium, gadolinium, gallium, germanium, gold, indium, iron, lutetium, manganese, magnesium, nickel, osmium, palladium, platinum, rhenium, rhodium, rubidium, ruthenium, samarium, silver, strontium, technetium, terbium, thallium, thorium, tin, yttrium, zinc, and oxidation states or isotopes thereof, in particular cobalt, copper, nickel, platinum, ruthenium, and zink, and oxidation states and isotopes thereof, preferably calcium (II), cobalt (II) and (III), copper (I) and (II), europium (III), iron (II) and (III), magnesium (II), manganese (II), nickel (II) and (III), palladium (II), platinum (II) and (V), ruthenium (II), (III), (IV), (VI) and (VI), samarium (III), terbium (III), zinc (II), or isotopes thereof, preferably cobalt (II) and (III), copper (I) and (II), nickel (II) and (III), zinc (II) and platinum (II) and (V), or isotopes thereof.

68. A chemical library comprising a plurality of test compounds of the following general formula I ##STR67## wherein F is N, O, S, Se or P; and G is N, O, S, Se or P; at least one of $(X)_n$ and $(Y)_m$ is present and if n is 0, then $--(X)_n--$ is absent, and if m is 0, then $--(Y)_m--$ is absent, and both n and m are not 0; R^1 and R^2, which are the same or different, are radicals preferably selected from the group consisting of: hydrogen, a C_{1-C15} alkyl, C_{2-C15} alkenyl, C_{2-C15} alkynyl, aryl, cycloalkyl, alkoxy, ester, --OCOR', --COOR', heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl group, an amine, imine, nitro, cyano, hydroxyl, alkoxy, ketone, aldelhyde, carboxylic acid, thiol, amide, sulfonate, sulfonic acid, sulfonamide, phosphonate, phosphonic acid group or a combination thereof, optionally substituted with one or more substituents selected from the same group as R^1 and/or a halogen such as F, Cl, Br or I; R' is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroalkenyl, substituted heteroalkenyl, heteroalkynyl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocycloalkyl, substituted heterocycloalkyl, heterocycloalkenyl or substituted heterocycloalkenyl; R^1 and/or R^2 optionally forming a fused ring together with any of P, $(X)_n$ or a part of $(X)_n$ G, $(Y)_m$ or a part of $(Y)_m$ or R^1 and R^2 themselves forming a fused ring; X and Y are the same or different and have the same meaning as R' such as, e.g., $--CH_2--$, $--C_{12}--CH2--$, $--CH_2--S--CH2--$, $--CH_2--N--CH2--$, --CH.dbd.CH--CH.dbd.CH--, $--(CH_2)_d--(Z)_e----(V)_f(W)_g(CH_2)_h--$, $--CH_2--O--CH2--$, wherein each of Z and W are independently C, S, O, N, Se or P and V is --CH-- or $--CH_2--$; $(X)_n$ and/or

$(Y)_m$ optionally being substituted with one or more substituents selected from the same group as R^1 and/or a halogen such as F, Cl, Br or I; n is 0 or an integer of 1-5, m is 0 or an integer of 1-5, e and/or g are an integer of 1-3, d, f and/or h are an integer of 1-7, the test compounds being in non-chelated form.

69. A chemical library comprising a plurality of metal ions selected from the group consisting of aluminium, antimony, arsenic, astatine, barium, beryllium, bismuth, boron, cadmium, calcium, cerium, cesium, chromium, cobalt, copper, dysprosium, erbium, europium, gadolinium, gallium, germanium, gold, hafnium, holmium, indium, iridium, iron, lanthanum, lead, lutetium, magnesium, manganese, mercury, molybdenum, neodymium, nickel, niobium, osmium, palladium, platinum, polonium, praseodymium, promethium, rhenium, rhodium, rubidium, ruthenium samarium, scandium, selenium, silicon, silver, strontium, tantalum, technetium, tellurium, terbium, thallium, thorium, thulium, tin, titanium, tungsten, vanadium, ytterbium, yttrium, zinc, zirconium, and oxidation states and isotopes thereof; in particular aluminium, antimony, barium bismuth, calcium, chromium, cobalt, copper, europium, gadolinium, gallium, germanium, gold, indium, iron, lutetium, manganese, magnesium, nickel, osmium, palladium, platinum, rhenium, rhodium, rubidium, ruthenium, samarium, silver, strontium, technetium, terbium, thallium thorium, tin, yttrium, zinc, and oxidation states or isotopes thereof; in particular cobalt, copper, nickel, platinum ruthenium, and zink and oxidation states and isotopes thereof, preferably calcium (II), cobalt (II) and (III), copper (I) and (II), europium (III), iron (II) and (III), magnesium (II), manganese (II), nickel (II) and (III), palladium (II), platinum (II) and (V), ruthenium (II), (III), (IV), (VI) and (VIII), samarium (III), terbium (III), zinc (II), or isotopes thereof preferably cobalt (II) and (III), copper (I) and (II), nickel (II) and (III), zinc (II) and platinum (II) and (V), or isotopes thereof.

70. A chemical library according to claim 67 or 68, wherein the molecular weight of the individual test compounds is at the most 2000, log P is at the most 7, the number of hydrogen bond donors is at the most 10 and the number of hydrogen bond acceptors is at the most 15.

71. A chemical library according to claim 70, wherein the molecular weight of the individual test compounds is at the most 1500 such as, e.g., at the most 1000 or at the most 500; log P is at the most 6 such as, e.g., at the most 5; the number of hydrogen bond donors is at the most 8 such as, e.g., at the most 7, 6 or 5; and the number of hydrogen bond acceptors is at the most 13 such as, e.g., 12, 11 or 10

72. A chemical library according to any of claims 67-71 for use in a drug discovery process according to any of claims 1-52.

73. Use of a test compound according to any of claims 53-66 in chelated form as either a stabilizing or as a destabilizing agent for di- or oligomerisation of a biological target molecule.

74. Use according to claim 73, wherein the biological target molecule is a membrane protein.

75. Use according to claim 74, wherein the membrane protein is 7TM.

76. Use of a test compound according to any of claims 53-66 in pharmacological knock-out experiments employing a biological target molecule in which a silent metal ion binding site has been created without affecting the binding action of an endogenous ligand for the biological target molecule with an aim of determining the effect of either an agonist or an **antagonist** on the physiological function of the metal ion site engineered receptor introduced into an animal by homologous gene replacement.

77. A method for characterising an orphan receptor, the method comprising (a) mutating the orphan receptor in such a way that at least one amino acid residue capable of binding a metal ion is introduced into the orphan receptor so as to obtain a metal ion binding site as an anchor point in the mutated orphan receptor, (b) contacting the mutated orphan receptor with a test compound which comprises a moiety including at least two heteroatoms for chelating a metal ion, under conditions permitting non-covalent binding of the test compound to the introduced metal ion binding site of the orphan receptor, and (c) monitoring the

binding of the test compound to the mutated orphan receptor by e.g. functional assays or through ligand binding assays.

78. A method according to claim 77 further comprising an optimization step in order to improve the affinity of the test compound.

79. Use of a test compound according to any of claims 53-66 as tracers in binding assays for orphan receptors.

L14 ANSWER 22 OF 56 USPATFULL on STN
2002:112926 Compounds specific to adenosine A1 receptors and uses thereof.
Castelhano, Arlindo L., New City, NY, UNITED STATES
McKibben, Bryan, White Plains, NY, UNITED STATES
Witter, David J., Putman Valley, NY, UNITED STATES
US 2002058667 A1 20020516
APPLICATION: US 2000-728316 A1 20001201 (9)
PRIORITY: US 1999-168803P 19991202 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A compound having the structure: ##STR281## wherein R_2 is a 5-6 membered aromatic ring; wherein R_3 and R_4 are independently H, or alkyl.

2. The compound of claim 1, having the structure: ##STR282##

3. The compound of claim 2, having the structure: ##STR283##

4. The compound of claim 2, having the structure: ##STR284##

5. The compound of claim 2, having the structure: ##STR285##

6. The compound of claim 2, having the structure: ##STR286##

7. A compound having the structure: ##STR287## wherein R_2 is a 5-6 membered aromatic ring; wherein R_3 and R_4 are independently H, or alkyl; with the proviso that R_2 is not 4-pyridyl.

8. The compound of claim 7, having the structure: ##STR288##

9. A compound having the structure: ##STR289## wherein R_2 is a substituted 5-6 membered aromatic ring; wherein R_3 and R_4 are independently H, or alkyl.

10. The compound of claim 9, having the structure: ##STR290##

11. A compound having the structure: ##STR291## wherein R_2 is a 5-6 membered aromatic ring; wherein X is oxygen, or sulfur.

12. The compound of claim 11, having the structure: ##STR292##

13. A compound having the structure: ##STR293## wherein R_2 is a 5-6 membered aromatic ring; wherein X is oxygen, or sulfur.

14. The compound of claim 13, having the structure: ##STR294##

15. A method for treating a disease associated with A_1 **adenosine receptor** in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claims 1, 7, 9, 11, or 13.

16. The method of claim 15, wherein the subject is a mammal.

17. The method of claim 16, wherein the mammal is a human.

18. The method of claim 15, wherein said A_1 **adenosine receptor** is associated with cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, branchoconstriction, neutropil chemotaxis, reflux condition, or ulcerative condition.

19. A water-soluble prodrug of the compound of claims 1, 7, 9, 11, or 13, wherein said water-soluble prodrug that is metabolized in vivo to produce an active drug which selectively inhibit A_1 **adenosine receptor**.

20. The prodrug of claim 19, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

21. A pharmaceutical composition comprising the prodrug of claim 19 and a pharmaceutically acceptable carrier.

22. A method for inhibiting the activity of an A_1 **adenosine receptor** in a cell, which comprises contacting said cell with a compound of claims 1, 7, 9, 11, or 13.

23. The method of claim 22, wherein the compound is an **antagonist** of said A_1 **adenosine receptor**.

24. The method of claim 22, wherein the cell is human cell.

25. The method of claim 22, wherein the compound is an **antagonist** of A_1 **adenosine receptors**.

26. The method of claim 15, wherein said disease is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

27. The method of claim 26, wherein the subject is a human.

28. The method of claim 26, wherein said compound is an **antagonist** of A_1 **adenosine receptors**.

29. A combination therapy for asthma, comprising the compound of claims 1, 7, 9, 11, or 13, and a steroid, β2 agonist, glucocoticoid, lucotriene **antagonist**, or anticolinegic agonist.

30. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claims 1, 7, 9, 11, or 13 and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

32. The pharmaceutical composition of claim 30, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

33. The pharmaceutical composition of claim 30, wherein said pharmaceutical composition is a systemic formulation.

34. The pharmaceutical composition of claim 30, wherein said pharmaceutical composition is a surgical irrigating solution.

35. A packaged pharmaceutical composition for treating a disease associated with A_1 **adenosine receptor** in a subject, comprising: (a) a container holding a therapeutically effective amount of the compound of claims 1, 7, 9, 11, or 13; and (b) instructions for using said compound for treating said disease in a subject.

36. A method of preparing compounds VI, VII, VIII, IX, or X, comprising the steps of a) reacting ##STR295## wherein P is a removable protecting group; b) treating the product of step a) under cyclization conditions to provide ##STR296## c) treating the product of step b) under suitable conditions to provide ##STR297## and d) treating the chlorinated product of step c) with NH_{2R1} to provide ##STR298## wherein R_1 is 2-(methylamino carbonylamino)-cyclohexyl, acetylamino ethyl, methylamino carbonylamino ethyl, or trans-4-hydroxy cyclohexyl; wherein R_2 is a four to six membered ring; and wherein R_3 and R_4 are independently H, or alkyl.

L14 ANSWER 23 OF 56 USPATFULL on STN
2002:109049 Method of treating airway diseases with combined administration of

A2B and A3 **adenosine receptor antagonists.**
Mustafa, S. Jamal, 419 Kempton Dr., Greenville, NC, United States 27834
US 6387913 B1 20020514
APPLICATION: US 2001-997948 20011130 (9)
PRIORITY: US 2000-251962P 20001207 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating an airway disease, airway inflammation, or both an airway disease and airway inflammation in a subject in need of such treatment, comprising concurrently administering to said subject an A_3 **adenosine receptor antagonist** and an A_{2B} **adenosine receptor antagonist,** in an amount effective to treat said disease.

2. A method according to claim 1, wherein said airway disease is asthma and inflammation.

3. A method according to claim 1, wherein said A_3 **adenosine receptor antagonist** is an antisense oligonucleotide.

4. A method according to claim 1, wherein said A_{2B} **adenosine receptor antagonist** is an antisense oligonucleotide.

5. A method according to claim 1, wherein said A_{2B} **adenosine receptor antagonist** is enprofylline.

6. A method according to claim 1, wherein said A_3 **adenosine receptor antagonist** is MRS 1220.

L14 ANSWER 24 OF 56 USPATFULL on STN
2002:81468 Modulation of human mast cell activation.
Pelleg, Amir, Haverford, PA, United States
Schulman, Edward S., Philadelphia, PA, United States
Duska Scientific Co., Haverford, PA, United States (U.S. corporation)
US 6372724 B1 20020416
WO 9842353 19981001
APPLICATION: US 1999-381692 19991202 (9)
WO 1998-US5922 19980324 19991202 PCT 371 date
PRIORITY: US 1997-41461P 19970325 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for modulating histamine release from stimulated human mast cells comprising contacting said cells with an effective amount of an agent which inhibits ATP binding to **P2-purinoceptors** on said cells.

2. A method according to claim 1 wherein the agent inhibits ATP binding to a **P2Y-purinoceptor** on said cells.

3. A method according to claim 2 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$ on said cells.

4. A method according to claim 2 wherein the agent is a **P2Y-purinoceptor antagonist.**

5. A method according to claim 2 wherein the agent is an allosteric modifier of a **P2Y-purinoceptor.**

6. A method according to claim 3 wherein the agent is a $P2Y_{1}$- or $P2Y_{2\text{-purinoceptor}}$ **antagonist.**

7. A method according to claim 6 wherein the **antagonist** is selected from the group consisting of adenosine-3'-phosphate-5'-phosphate, adenosine-3'-phosphate-5'-phosphosulfate, and a combination thereof.

8. A method according to claim 3 wherein the agent is an allosteric modifier of the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$.

9. A method according to claim 1 wherein the stimulated mast cells comprise immunologically stimulated mast cells.

10. A method according to claim 9 wherein the immunologically stimulated mast cells comprise lung, nose, eye, gut or joint mast cells.

11. A method according to claim 10 wherein the immunologically stimulated mast cells comprise lung mast cells.

12. A method according to claim 11 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$ on said immunologically stimulated lung mast cells.

13. A method for treating a human subject for a disorder characterized by undesirable release of histamine from immunologically stimulated lung mast cells comprising administering to the subject an effective amount of an agent which inhibits ATP binding to **P2-purinoceptors** on said mast cells.

14. A method according to claim 13 wherein the agent inhibits ATP binding to a **P2Y-purinoceptor** on said mast cells.

15. A method according to claim 14 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or the $P2Y_{2\text{-purinoceptor}}$ on said mast cells.

16. A method according to claim 15 wherein the agent is a $P2Y_{1}$- or $P2Y_{2\text{-purinoceptor}}$ **antagonist**.

17. A method according to claim 16 wherein the **antagonist** is selected from the group consisting of adenosine-3'-phosphate-5'-phosphate, adenosine-30'-phosphate-5'-phosphosulfate, and combinations thereof.

18. A method according to claim 13 wherein the disorder is an allergy.

19. A method according to claim 13 wherein the disorder is asthma.

20. A method according to claim 13 wherein the disorder is inflammatory lung disease.

21. A method for treating a human subject for a bronchoconstriction caused by histamine release from stimulated lung mast cells comprising administering to the subject an effective amount of an agent which inhibits ATP binding to **P2-purinoceptors** on said mast cells.

22. A method according to claim 21 wherein the agent inhibits ATP binding to a **P2Y-purinoceptor** on said mast cells.

23. A method according to claim 22 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$ on said mast cells.

L14 ANSWER 25 OF 56 USPATFULL on STN
2002:69804 Methods of culturing and encapsulating pancreatic islet cells.
Opara, Emmanuel C., Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 6365385 B1 20020402
APPLICATION: US 1999-453348 19991201 (9)
DOCUMENT TYPE: Utility; GRANTED.

CLM What is claimed is:

1. A method of treating isolated pancreatic islet cells, comprising: (a) culturing said cells in a medium containing at least one compound selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic; then (b) microencapsulating said cells in a biocompatible microcapsule comprising a core and a semipermeable outer membrane, to provide a microcapsule containing living cells therein; and then (c) incubating said microcapsule containing living cells therein with a physiologically acceptable salt to increase the durability of the microcapsule, while retaining the physiological responsiveness of the living cells contained in the microcapsule to produce microencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month.

2. A method according to claim 1, wherein said medium contains at least two compounds selected from the group consisting of an antioxidant, an

anti-cytokine, an anti-endotoxin, and an antibiotic.

3. A method according to claim 1, wherein said medium contains at least three compounds selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

4. A method according to claim 1, wherein said medium contains at least one each of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

5. A method according to claim 1, wherein said antioxidant is selected from the group consisting of glutathione, glutathione monoester, N-acetylcysteine, superoxide dismutase, catalase, vitamin E, α-tocopherol, lipoic acid, lazaroids, butylated hydroxyanisole (BHA), and vitamin K.

6. A method according to claim 1, where said microcapsule comprises a polysaccharide gum surrounded by a semipermeable membrane.

7. A method according to claim 1 where said microcapsule comprises alginate in combination with polylysine, polyornithine, and combinations thereof.

8. A method according to claim 1 wherein said core comprises alginate and contains said cells.

9. A method according to claim 8 wherein said core is gelled.

10. A method according to claim 8 wherein said core is not gelled.

11. A method according to claim 1 wherein said microcapsule has a diameter of from about 50 μm to about 2 mm.

12. A method according to claim 1 wherein said microcapsule has a diameter of from about 200 μm to about 1000 μm.

13. A method according to claim 1 wherein said microcapsule has a diameter of from about 300 μm to about 700 μm.

14. A method according to claim 1, wherein said physiologically acceptable salt is a sulfate salt.

15. A method according to claim 1, wherein said physiologically acceptable salt is selected from the group consisting of sodium sulfate and potassium sulfate.

16. Microencapsulated islet cells produced by a method according to claim 1.

17. A method of preparing microencapsulated pancreatic islet cells comprising: (a) culturing pancreatic islet cells in a first cell culture medium comprising at least one compound selected from the group consisting of: antioxidants, anti-cytokines, anti-endotoxins, and antibiotics; then (b) encapsulating pancreatic islet cells in a biocompatible microcapsule comprising a core and a semipermeable outer membrane, where said islet cells are present in said core, and (c) culturing said cells while in said microcapsule in a second medium comprising at least one compound selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic; and then (d) incubating said microcapsule containing living cells therein with a physiologically acceptable salt to increase the durability of the microcapsule, while retaining the physiological responsiveness of the living cells contained in the microcapsule to produce microcencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month.

18. A method according to claim 17, wherein said culture media contain at least two compounds selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

19. A method according to claim 17, wherein said culture media contains

at least three compounds selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

20. A method according to claim 17, wherein said culture media contains at least one each of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

21. A method according to claim 17, wherein said antioxidant is selected from the group consisting of glutathione, glutathione monoester, N-acetylcysteine, superoxide dismutase, catalase, vitamin E, α-tocopherol, lipoic acid, lazaroids, butylated hydroxyanisole (BHA), and vitamin K.

22. A method according to claim 17, wherein said anti-endotoxin is selected from the group consisting of L-NG-Monomethylarginine (L-NMMA), lactoferrin, N-acetylcysteine (NAC), **adenosine receptor antagonists** and anti-lipopolysaccharide compounds.

23. A method according to claim 17, wherein said anti-cytokine is selected from the group consisting of dimethylthiourea, citiolone, pravastatin sodium, L-NG-Monomethylarginine (L-NMMA), lactoferrin and 4-methylprednisolone.

24. A method according to claim 17, where said microcapsule core comprises a polysaccharide gum.

25. A method according to claim 17 where said microcapsule comprises alginate in combination with polylysine, polyornithine, or combinations thereof.

26. A method according to claim 17 wherein said core comprises alginate and contains said cells.

27. A method according to claim 26 wherein said core is gelled.

28. A method according to claim 26 wherein said core is not gelled.

29. A method according to claim 17 wherein said microcapsule has a diameter of from about 50 μm to about 2 mm.

30. A method according to claim 17 wherein said microcapsule has a diameter of from about 200 μm to about 1000 μm.

31. A method according to claim 17 wherein said microcapsule has a diameter of from about 300 μm to about 700 μm.

32. A method according to claim 17, wherein said physiologically acceptable salt is a sulfate salt.

33. A method according to claim 17, wherein said physiologically acceptable salt is selected from the group consisting of sodium sulfate and potassium sulfate.

34. Microencapsulated islet cells produced by a method according to claim 17.

L14 ANSWER 26 OF 56 USPATFULL on STN
2002:48606 Irrigation solution and method for inhibition of pain and inflammation.
Demopulos, Gregory A., Mercer Island, WA, UNITED STATES
Pierce-Palmer, Pamela, San Francisco, CA, UNITED STATES
Herz, Jeffrey M., Mill Creek, WA, UNITED STATES
Omeros Medical Systems (U.S. corporation)
US 2002028798 A1 20020307
APPLICATION: US 2001-839633 A1 20010420 (9)
PRIORITY: US 1998-105026P 19981020 (60)
US 1998-105029P 19981020 (60)
US 1998-105044P 19981020 (60)
US 1998-105166P 19981021 (60)
US 1998-107256P 19981105 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of preemptively inhibiting pain and inflammation at a wound

during a surgical procedure, comprising delivering to a wound during a surgical procedure a solution comprising at least one pharmacological agent selected from the group consisting of a mitogen-activated protein kinase (MAPK) inhibitor, an $\alpha_{2\text{-receptor}}$ agonist, a neuronal nicotinic acetylcholine receptor agonist, a cyclooxygenase-2 (COX-2) inhibitor, a soluble receptor and mixtures thereof, wherein the solution is applied locally and perioperatively to the surgical site.

2. The method of claim 1, wherein the pharmacological agent is a MAPK inhibitor selected from the group consisting of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)-1H-imidazole, [4-(3-iodophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)-1H-imidazole], [4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4- pyridyl)-1H-imidazole], [4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole], and 2'-Amino-3'-methoxyflavone.

3. The method of claim 1, wherein the pharmacological agent is an $\alpha_{2\text{-receptor}}$ agonist selected from the group consisting of clonidine; dexmedetomidine; oxymetazonline; (R)-(-)-3'-(2-amino-1-hydroxyethyl)-4'-fluoro-methanesulfoanilide (NS-49); 2-[(5-methylbenz-1-ox-4-azin-6-yl)imino]imidazoline (AGN-193080); AGN 191103; AGN 192172; 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (UKI4304); 5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo [4,5-d]azepin-2-amine (BHT920); 6-ethyl-5,6,7,8-tetrahydro-4H-oxaazolo[4,5-d]azepin-2-amine (BHT933); and 5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphyl-imidazoline (A-54741).

4. The method of claim 1, wherein the pharmacological agent is a neuronal nicotinic acetylcholine receptor agonist selected from the group consisting of (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594); (S)-5-(2-azetidinyl- methoxy)-2-chloropyridine (S-enatiomer of ABT-594); 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine (ABT-089); (R)-5-(2-Azetidinylmethoxy)-2-chloropyridine (ABT-594); (2,4)-Dimethoxy-benzylidene anabaseine (GTS-21); SBI-1765F; RJR-2403; 3-((1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine (A-84543); 3-(2(S)-azetidinylmethoxy)pyridine (A-85380); (+)-anatoxin-A and (-)anatoxin-A (1R)-1-(9-Azabicyclo [4.2.2]non-2-en-2-yl)-ethanoate fumarate, and (R,S)-3-pyridyl-1-methyl-2-(3-pyridyl)azetidine (MPA).

5. The method of claim 1, wherein the pharmacological agent is a COX-2 inhibitor selected from the group consisting of celecoxib, meloxicam, nimesulide, nimesulide, diclofenac, flosulide, N-[2-(cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)-phenyl]pyrazole, DuP 697, SC-58451, RS-57067, SC-57666 and L-745,337.

6. The method of claim 1, wherein the pharmacological agent is a soluble receptor selected from the group consisting of tumor necrosis factor (TNF) soluble receptors, interleukin-1 (IL-1) cytokine receptors, class I cytokine receptors, and receptor tyrosine kinases.

7. The method of claim 1, wherein the solution further comprises at least one additional pain/inflammation inhibitory agent selected to act on a different molecular target than the pharmacological agent.

8. The method of claim 1, comprising continuously applying the solution to the wound.

9. The method of claim 8, comprising continuously irrigating the wound with the solution.

10. The method of claim 1, wherein the solution is applied by irrigation of the wound.

11. The method of claim 1, wherein the perioperative application of the solution comprises intraprocedural application together with preprocedural or postprocedural application of the solution.

12. The method of claim 1, wherein the perioperative application of the solution comprises preprocedural, intraprocedural and postprocedural application of the solution.

13. The method of claim 1, wherein each of the pharmacological agent in the solution is delivered locally at a concentration of no greater than 100,000 nanomolar.

14. The method of claim 7, wherein the at least one additional pain/inflammation inhibitory agent is selected from the group consisting of: serotonin receptor **antagonists**; serotonin receptor agonists; histamine receptor **antagonists**; bradykinin receptor **antagonists**; kallikrein inhibitors; tachykinin receptor **antagonists** including neurokinin$_1$ receptor subtype **antagonists** and neurokinin$_2$ receptor subtype **antagonists**; calcitonin gene-related peptide receptor **antagonists**; interleukin receptor **antagonists**; phospholipase inhibitors including PLA_2 isoform inhibitors and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor **antagonists** including eicosanoid EP-1 receptor subtype **antagonists** and eicosanoid EP-4 receptor subtype **antagonists** and thromboxane receptor subtype **antagonists**; leukotriene receptor **antagonists** including leukotriene B_4 receptor subtype **antagonists** and leukotriene D_4 receptor subtype **antagonists**; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinoceptor agonists and **antagonists** including P_{2Y} receptor agonists and **P2X receptor antagonists**; and ATP-sensitive potassium channel openers.

15. A solution for use in the preemptive inhibition of pain and inflarnmation at a wound during a surgical procedure, comprising at least one pharmacological agent selected from the group consisting of a mitogen-activated protein kinase (MAPK) inhibitor, an $\alpha_{2\text{-receptor}}$ agonist, a neuronal nicotinic acetylcholine receptor agonist, a cyclooxygenase-2 (COX-2) inhibitor, a soluble receptor and mixtures thereof, in a liquid carrier, the concentration of said pharmacological agent within the solution being the concentration of that agent which is desired to be delivered locally, in the absence of metabolic transformation, to a wound in order to achieve a predetermined level of inhibitory effect at the wound.

16. The solution of claim 16, wherein the pharmacological agent is selected from the group consisting of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)-1H-imidazole, [4-(3-iodophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-mirdazole], [4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4- pyridyl)-1H-imidazole], [4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-irnidazole], 2'-Amino-3'-methoxyflavone, clonidine; dexmedetomidine; oxymetazonline; (R)-(-)-3'-(2-amino-1-hydroxyethyl)-4'-fluoro-methanesulfoanilide (NS-49); 2-[(5-methylbenz-1-ox-4-azin-6-yl)imino]imidazoline (AGN-193080); AGN 191103; AGN 192172; 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (UK14304); 5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo [4,5-d]azepin-2-amine (BHT920); 6-ethyl-5,6,7,8-tetrahydro-4H-oxaazolo[4,5-d]azepin-2-amine (BHT933); 5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphyl-imidazoline (A-54741), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594); (S)-5-(2-azetidinyl-methoxy)-2-chloropyridine (S-enatiomer of ABT-594); 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine (ABT-089); (R)-5-(2-Azetidinylmethoxy)-2-chloropyridine (ABT-594); (2,4)-Dimethoxy-benzylidene anabaseine (GTS-21); SBI-1765F; RJR-2403; 3-((1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine (A-84543); 3-(2(S)-azetidinylmethoxy)pyridine (A-85380); (+)-anatoxin-A and (-)anatoxin-A (IR)- 1 -(9-Azabicyclo [4.2.2]non-2-en-2-yl)-ethanoate fumarate, (R,S)-3-pyridyl-1-methyl-2-(3-pyridyl)azetidine (MPA), celecoxib, meloxicam, nimesulide, nimesulide, diclofenac, flosulide, N-[2-(cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)phenyl]pyrazole, DuP 697, SC-58451, RS-57067, SC-57666, L-745,337, tumor necrosis factor (TNF) soluble receptors, interleukin-1 (IL-1) cytokine receptors, class I cytokine receptors, receptor tyrosine kinases and mixtures thereof.

17. The solution of claim 15, which further comprises at least one additional pain/inflammation inhibitory agent selected to act on a different molecular target than the at least one pharmacological agent.

18. The solution of claim 17, wherein the pharmacological agent and each of the additional pain/inflammation inhibitory agents in the solution is included at a concentration of no greater than 100,000 nanomolar, adjusted for dilution in the absence of metabolic transformation, at an intended local delivery site.

19. The solution of claim 17, wherein the at lease one additional

pain/inflammation inhibitory agents are selected from the group consisting of serotonin receptor **antagonists**; serotonin receptor agonists; histamine receptor **antagonists**; bradykinin receptor **antagonists**; kallikrein inhibitors; tachykinin receptor **antagonists** including neurokinin, receptor subtype **antagonists** and neurokinin$_2$ receptor subtype **antagonists**; calcitonin gene-related peptide receptor **antagonists**; interleukin receptor **antagonists**; phospholipase inhibitors including PLA_2 isoform inhibitors and PLC, isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor **antagonists** including eicosanoid EP-1 receptor subtype **antagonists** and eicosanoid EP-4 receptor subtype **antagonists** and thromboxane receptor subtype **antagonists**; leukotriene receptor **antagonists** including leukotriene B_4 receptor subtype **antagonists** and leukotriene D_4 receptor subtype **antagonists**; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinoceptor agonists and **antagonists** including P_{2Y} receptor agonists and P_{2X} receptor **antagonists**; and ATP-sensitive potassium channel openers.

L14 ANSWER 27 OF 56 USPATFULL on STN
2002:48590 Pyrrolo [2, 3d] pyrimidine compositions and their use.
Castelhano, Arlindo L., New City, NY, UNITED STATES
McKibben, Bryan, White Plains, NY, UNITED STATES
Witter, David J., Putnam Valley, NY, UNITED STATES
US 2002028782 A1 20020307
APPLICATION: US 2000-728229 A1 20001201 (9)
PRIORITY: US 1998-87702P 19980602 (60)
US 1999-123216P 19990308 (60)
US 1999-126527P 19990326 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for treating a N-6 substituted 7-deazapurine responsive state in a mammal, comprising administering to a mammal a therapeutically effective amount of a N-6 substituted 7-deazapurine, such that treatment of a N-6 substituted 7-deazapurine responsive state in the mammal occurs.

2. The method of claim 1, wherein said N-6 substituted 7-deazapurine responsive state is a disease state, wherein the disease state is a disorder mediated by adenosine.

3. The method of claim 1, wherein said N-6 substituted 7 deazapurine is not N-6 benzyl or N-6 phenylethyl substituted.

4. The method of claim 2, wherein said disease state is a central nervous system disorder, a cardiovascular disorder, a renal disorder, an inflammatory disorder, an allergic disorder, a gastrointestinal disorder, an eye disorder or a respiratory disorder.

5. The method of claim 1, wherein said N-6 substituted 7-deazapurine has the formula I: ##STR177## wherein R_1 and R_2 are each independently a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or together form a substituted or unsubstituted heterocyclic ring; R_3 is a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; R_4 is a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; R_5 and R_6 are each independently a halogen atom, a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or R_4 and R_5 or R_5 and R_6 together form a substituted or unsubstituted heterocyclic or carbocyclic ring.

6. A method for modulating an **adenosine receptor** in a mammal, comprising administering to a mammal a therapeutically effective amount of a N-6 substituted 7-deazapurine, such that modulation of an **adenosine receptor** in the mammal occurs.

7. The method of claim 6, wherein said **adenosine receptor** is A_1, A_2, A_{2a}, A_{2b}, or A_3.

8. The method of claim 6, wherein said **adenosine receptor** is associated with a central nervous system disorder, a cardiovascular

disorder, a renal disorder, an inflammatory disorder, a gastrointestinal disorder, an eye disorder, an allergic disorder or a respiratory disorder.

9. The method of claim 6, wherein said N-6 substituted 7-deazapurine has the formula I: ##STR178## wherein R_1 and R_2 are each independently a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or together form a substituted or unsubstituted heterocyclic ring; R_3 is a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; R_4 is a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; and R_5 and R_6 are each independently a halogen atom, a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or R_4 and R_5 or R_5 and R_6 together form a substituted or unsubstituted heterocyclic or carbocyclic ring.

10. A method for treating asthma in a mammal, comprising administering to a mammal a therapeutically effective amount of a N-6 substituted 7-deazapurine, such that treatment of asthma in the mammal occurs.

11. An N-6 substituted 7-deazapurine having the formula I: ##STR179## wherein R_1 and R_2 are each independently a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or together form a substituted or unsubstituted heterocyclic ring, provided that both R_1 and R_2 are both not hydrogen atoms or that neither R_1 or R_2 is 1-phenylethyl; R_3 is a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; R_4 is a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; and R_5 and R_6 are each independently a halogen atom, a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or R_4 and R_5 or R_5 and R_6 together form a substituted or unsubstituted heterocyclic or carbocyclic ring, provided R_4 is not 1-phenylethyl, and pharmaceutically acceptable salts thereof.

12. A deazapurine of claim 11, wherein: R_1 is hydrogen; R_2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkyl, or R_1 and R_2 together form a substituted or unsubstituted heterocyclic ring; R_3 is unsubstituted or substituted aryl; R_4 is hydrogen; and R_5 and R_6 are each independently hydrogen or alkyl, and pharmaceutically acceptable salts thereof.

13. The deazapurine of claim 12, wherein R_2 is substituted or unsubstituted cycloalkyl.

14. The deazapurine of claim 13, wherein R_1 and R_4 are hydrogen, R_3 is unsubstituted or substituted phenyl, and R_5 and R_6 are each alkyl.

15. The deazapurine of claim 14, wherein R_2 is substituted with at least one hydroxy group.

16. The deazapurine of claim 15, wherein R_2 is mono-hydroxycyclopentyl.

17. The deazapurine of claim 15, wherein R_2 is mono-hydroxycyclohexyl.

18. The deazapurine of claim 14, wherein R_2 is substituted with --NH--C(.dbd.O)E, wherein E is substituted or unsubstituted C_{1-C4} alkyl.

19. The deazapurine of claim 18, wherein E is alkylamine.

20. The deazapurine of claim 19, wherein E is ethylamine.

21. The deazapurine of claim 12, wherein R_1 and R_2 together form a substituted or unsubstituted heterocyclic ring.

22. The deazapurine of claim 21, wherein said heterocyclic ring is substituted with an amine.

23. The deazapurine of claim 21, wherein said heterocyclic ring is substituted with acetamido.

24. The deazapurine of claim 12, wherein R_2 is --A--NHC(.dbd.O)B, wherein A is unsubstituted C_{1-C4} alkyl, and B is substituted or unsubstituted C_{1-C4} alkyl.

25. The deazapurine of claim 24, wherein R_1 and R_4 are hydrogen, R_3 is unsubstituted or substituted phenyl, and R_5 and R_6 are each alkyl.

26. The deazapurine of claim 25, wherein A is CH_{2CH2}.

27. The deazapurine of claim 25, wherein A is $CH_{2CH2CH2}$.

28. The deazapurine of claim 25, wherein A is $CH_{2CH2CH2CH2}$.

29. The deazapurine of claim 25, wherein B is methyl.

30. The deazapurine of claim 25, wherein B is aminoalkyl.

31. The deazapurine of claim 30, wherein B is aminomethyl.

32. The deazapurine of claim 30, wherein B is aminoethyl.

33. The deazapurine of claim 25, wherein B is alkylamino.

34. The deazapurine of claim 33, wherein B is methylamino.

35. The deazapurine of claim 33, wherein B is ethylamino.

36. The deazapurine of claim 25, wherein B is substituted or unsubstituted cycloalkyl.

37. The deazapurine of claim 36, wherein B is cyclopropyl.

38. The deazapurine of claim 36, wherein B is 1-amino-cyclopropyl.

39. The deazapurine of claim 12, wherein R_3 is substituted or unsubstituted phenyl.

40. The deazapurine of claim 39, wherein R_5 and R_6 are each alkyl.

41. The deazapurine of claim 40, wherein R_3 is unsubstituted phenyl.

42. The deazapurine of claim 40, wherein R_3 is substituted phenyl.

43. The deazapurine of claim 42, wherein R_3 is phenyl with at least one substituent.

44. The deazapurine of claim 43, wherein R_3 is o-, m- or p-chlorophenyl.

45. The deazapurine of claim 43, wherein R_3 is an o-, m- or p-fluorophenyl.

46. The deazapurine of claim 12, wherein R_3 is substituted or unsubstituted heteroaryl.

47. The deazapurine of claim 46, wherein R_5 and R_6 are each alkyl.

48. The deazapurine of claim 47, wherein R_3 is selected from the group consisting of pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, triazolyl, thioazolyl, oxazolyl, oxadiazolyl, furanyl, methylenedioxyphenyl and thiophenyl.

49. The deazapurine of claim 48, wherein R_3 is 2-pyridyl, 3-pyridyl, or 4-pyridyl.

50. The deazapurine of claim 48, wherein R_3 is 2-pyrimidyl or 3-pyrimidyl.

51. The deazapurine of claim 12, wherein R_5 and R are each hydrogen.

52. The deazapurine of claim 12, wherein R_5 and R_6 are each methyl.

53. The deazapurine of claim 12, wherein said compound is 4-(cis-3-hydroxycyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

54. The deazapurine of claim 12, wherein said compound is 4-(cis-3-(2-aminoacetoxy)cyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine trifluoroacetic acid salt.

55. The deazapurine of claim 12, wherein said compound is 4-(3-acetamido)piperidinyl-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

56. The deazapurine of claim 12, wherein said compound is 4-(2-N'-methylureapropyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

57. The compound of claim 12, wherein said compound is 4-(2-acetamidobutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

58. The deazapurine of claim 13, wherein said compound is 4-(2-N'-methylureabutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

59. The deazapurine of claim 12, wherein said compound is 4-(2-aminocyclopropylacetamidoethyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

60. The deazapurine of claim 12, wherein said deazapurine is 4-(trans-4-hydroxycyclohexyl)amino-2-(3-chlorophenyl)-7H-pyrrolo[2,3d]pyrimidine.

61. The deazapurine of claim 12, wherein said deazapurine is 4-(trans-4-hydroxycyclohexyl)amino-2-(3-fluorophenyl)-7H-pyrrolo[2,3d]pyrimidine.

62. The deazapurine of claim 12, wherein said deazapurine is 4-(trans-4-hydroxycyclohexyl)amino-2-(4-pyridyl)-7H-pyrrolo[2,3d]pyrimidine.

63. A deazapurine having the formula II: ##STR180## wherein X is N or CR_6; R_1 and R_2 are each independently hydrogen, or substituted or unsubstituted alkoxy, aminoalkyl, alkyl, aryl, or alkylaryl, or together form a substituted or unsubstituted heterocyclic ring, provided that both R_1 and R_2 are both not hydrogen; R_3 is substituted or unsubstituted alkyl, arylalkyl, or aryl; R_4 is hydrogen or substituted or unsubstituted C_{1-C6} alkyl; L is hydrogen, substituted or unsubstituted alkyl, or R_4 and L together form a substituted or unsubstituted heterocyclic or carbocyclic ring; R_6 is hydrogen, substituted or unsubstituted alkyl, or halogen; Q is CH_2, O, S, or NR_7, wherein R_7 is hydrogen or substituted or unsubstituted C_{1-C6} alkyl; and W is unsubstituted or substituted alkyl, cycloallyl, alkynyl, aryl, arylalkyl, biaryl, heteroaryl, substituted carbonyl, substituted thiocarbonyl, or substituted sulfonyl; provided that if R_3 is pyrrolidino, then R_4 is not methyl.

64. The deazapurine of claim 58 having the formula III: ##STR181## wherein Q is CH_2, O, S, or NH.

65. The deazapurine of claim 64, wherein R_4 is hydrogen, L is hydrogen or methyl and R_3 is unsubstituted or substituted aryl.

66. The deazapurine of claim 65, wherein W is substituted or unsubstituted aryl, 5- or 6-member heteroaryl, or biaryl.

67. The deazapurine of claim 66, wherein W is substituted with one or more substituents selected from the group consisting of halogen, hydroxy, alkoxy, amino, aminoalkyl, aminocarboxyamide, CN, CF_3, CO_{2R8}, $CONHR_8$, $CONR_{8R9}$, SOR_8, SO_{2R8}, and SO_{2NR8R9}, wherein R_8 and R_9 are each independently hydrogen, or substituted or unsubstituted alkyl, cycloalkyl, aryl, or arylalkyl.

68. The deazapurine of claim 66, wherein W is methylenedioxyphenyl.

69. The deazapurine of claim 66, wherein W is substituted or unsubstituted phenyl.

70. The deazapurine of claim 66, wherein W is a substituted or unsubstituted 5-membered heteroaryl ring.

71. The deazapurine of claim 66, wherein W is selected from the group consisting of pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, triazolyl, thioazolyl, oxazolyl, oxadiazolyl, pyrazolyl, furanyl, and thiophenyl

72. The deazapurine of claim 71, wherein Q is NH, and W is a 3-pyrazolo ring which is unsubstituted or N-substituted by substituted or unsubstituted alkyl, cycloalkyl, aryl, or arylalkyl.

73. The deazapurine of claim 71, wherein Q is oxygen, and W is a 2-thiazolo ring which is unsubstituted or substituted by substituted or unsubstituted alkyl, cycloalkyl, aryl, or arylalkyl.

74. The deazapurine of claim 66, wherein W is a 6-member heteroaryl ring.

75. The deazapurine of claim 74, wherein W is selected from the group consisting of 2-pyridyl, 3-pyridyl, and 4-pyridyl.

76. The deazapurine of claim 74, wherein W is selected from the group consisting of 2-pyrimidyl, 4-pyrimidyl, and 5-pyrimidyl.

77. The deazapurine of claim 65, wherein W is substituted or unsubstituted alkyl, cycloalkyl, alkynyl or arylalkyl.

78. The deazapurine of claim 77, wherein W is alkynyl.

79. The deazapurine of claim 78, wherein W is substituted with one or more substituents selected from the group consisting of halogen, hydroxy , substituted or unsubstituted alkyl, cycloalkyl, aryl, or arylalkyl, or NHR_{10} wherein R_{10} is hydrogen, or substituted or unsubstituted alkyl, cycloalkyl, aryl, or arylalkyl.

80. The deazapurine of claim 77, wherein W is substituted or unsubstituted cyclopentyl.

81. The deazapurine of claim 65, wherein W is $--(CH_2)_{a--}C(.dbd.O)Y$ or $--(CH_2)_{a--c}(.dbd.S)Y$, wherein a is 0, 1, 2 or 3, Y is aryl, alkyl, arylalkyl, cycloalkyl, heteroaryl, NHR_{11R12}, or, provided that Q is NH, OR_{13}, and wherein R_{11}, R_{12} and R_{13} are each independently hydrogen, or unsubstituted or substituted alkyl, aryl, arylalkyl, or cycloalkyl.

82. The deazapurine of claim 81 wherein a is 1.

83. The deazapurine of claim 81, wherein Y is a 5- or 6-member heteroaryl ring.

84. The deazapurine of claim 65, wherein W is $--(CH_2)_{b--}S(.dbd.O)_jY$, wherein j is 1 or 2, b is 0, 1, 2, or 3, Y is aryl, alkyl, arylalkyl, cycloalkyl, heteroaryl, NHR_{14R15}, or, provided that Q is NH, OR_{16}, and wherein R_{14}, R_{15}, and R_{16} are each independently hydrogen, or unsubstituted or substituted alkyl, aryl, arylalkyl, or cycloalkyl.

85. The deazapurine of claim 64, wherein R_3 is selected from the group consisting of substituted and unsubstituted phenyl, pyridyl,

pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, triazolyl, thioazolyl, oxazolyl, oxadiazolyl, pyrazolyl, furanyl, methylenedioxyphenyl, and thiophenyl.

86. The deazapurine of claim 85, wherein R_3 is unsubstituted phenyl.

87. The deazapurine of claim 85, wherein R_3 is phenyl with at least one substituent.

88. The deazapurine of claim 87, wherein said substituent is selected from the group consisting of hydroxyl, alkoxy, alkyl, and halogen.

89. The deazapurine of claim 88, wherein said substituent is halogen.

90. The deazapurine of claim 89, wherein R_3 is o-, m-, or p-fluorophenyl.

91. The deazapurine of claim 89, wherein R_3 is o-, m-, or p-chlorophenyl.

92. The deazapurine of claim 88, wherein R_3 is alkyl substituted phenyl.

93. The deazapurine of claim 92, wherein R_3 is tolyl.

94. The deazapurine of claim 88, wherein R_3 is alkoxy substituted phenyl.

95. The deazapurine of claim 94, wherein R_3 is methoxy phenyl.

96. The deazapurine of claim 85, wherein R_3 is a 2-, 3-, or 4-pyridyl.

97. The deazapurine of claim 85, wherein R_3 is a 2- or 3-pyrimidyl.

98. The deazapurine of claim 64, wherein R_6 is hydrogen or C_{1-C3} alkyl.

99. The deazapurine of claim 98, wherein R_6 is hydrogen.

100. The deazapurine of claim 64, wherein R_1 is hydrogen, and R_2 is substituted or unsubstituted alkyl or alkoxy, substituted or unsubstituted alkylamine, arylamine, or alkylarylamine, substituted or unsubstituted aminoalkyl, amino aryl, or aminoalkylaryl, substituted or unsubstituted alkylamide, arylamide or alkylarylamide, substituted or unsubstituted alkylsulfonamide, arylsulfonamide or alkylarylsulfonamide, substituted or unsubstituted alkylurea, arylurea or alkylarylurea, substituted or unsubstituted alkylcarbamate, arylcarbamate or alkylarylcarbamate, or substituted or unsubstituted alkylcarboxylic acid, arylcarboxylic acid or alkylarylcarboxylic acid.

101. The deazapurine of claim 100, wherein R_2 is substituted or unsubstituted cycloalkyl.

102. The deazapurine of claim 101, wherein R_2 is mono- or dihydroxy-substituted cyclohexyl.

103. The deazapurine of claim 102, wherein R_2 is monohydroxy-substituted cyclohexyl.

104. The deazapurine of claim 101, wherein R_2 is mono- or dihydroxy-substituted cyclopentyl.

105. The deazapurine of claim 104, wherein R_2 is monohydroxy-substituted cyclopentyl.

106. The deazapurine of claim 100, wherein R_2 is ##STR182## wherein A is C_{1-C6} alkyl, C_{3-C7} cycloalkyl, a chain of one to seven atoms, or a ring of three to seven atoms, optionally substituted with C_{1-C6} alkyl, halogens, hydroxyl, carboxyl, thiol, or amino groups; B is methyl, $N(Me)_2$, $N(Et)_2$, NHMe, NHEt, $(CH_2)_{rNH3}+$, $NH(CH_2)_{rCH3}$,

$(CH_2)_rNH_2$, $(CH_2)_rCHCH_3NH_2$, $(CH_2)_rNHMe$, $(CH_2)_rOH$, CH_2CN, $(CH_2)_mCO_2H$, $CHR_{18}R_{19}$, or CHMeOH, wherein r is an integer from 0 to 2, m is 1 or 2, R_{18} is alkyl, R_{19} is NH_3^+ or CO_{2H} or R_{18} and R_{19} together are: ##STR183## wherein p is 2 or 3; and R_{17} is C_{1-C6} alkyl, C_{3-C7} cycloalkyl, a chain of one to seven atoms, or a ring of three to seven atoms, optionally substituted with C_{1-C6} alkyl, halogens, hydroxyl, carboxyl, thiol, or amino groups.

107. The deazapurine of claim 106, wherein A is unsubstituted or substituted C_{1-C6} alkyl.

108. The deazapurine of claim 106, wherein B is unsubstituted or unsubstituted C_{1-C6} alkyl.

109. The deazapurine of claim 106, wherein R_2 is --A--NHC(.dbd.O)B.

110. The deazapurine of claim 109, wherein A is $--CH_{2CH2}--$ and B is methyl.

111. The deazapurine of claims 11, 12, 65 or 66, which comprises a water-soluble prodrug that is metabolized in vivo to an active drug.

112. The deazapurine of claim 111, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

113. The deazapurine of claim 111, wherein R_2 is cycloalkyl substituted with $--OC(O)(Z)NH_2$, wherein Z is a side chain of a naturally or unnaturally occurring amino acid, or analog thereof, an α, β, γ, or ω amino acids, or a dipeptide.

114. The deazapurine of claim 113, wherein Z is a side chain of glycine, alanine, valine, leucine, isoleucine, lysine, α-methylalanine, aminocyclopropane carboxylic acid, azetidine-2-carboxylic acid, β-alanine, γ-aminobutyric acid, alanine-alanine, or glycine-alanine.

115. The deazapurine of claim 64, wherein R_1 and R_2 together are: ##STR184## wherein n is 1 or 2, and wherein the ring may be optionally substituted with one or more hydroxyl, amino, thiol, carboxyl, halogen, CH_{2OH}, CH_{2NHC}(.dbd.O)alkyl, or CH_{42NHC}(.dbd.O)NHalkyl groups.

116. The deazapurine of claim 115, wherein n is 1 or 2 and said ring is substituted with --NHC(.dbd.O)alkyl.

117. The deazapurine of claim 64, wherein R_1 is hydrogen, R_2 is substituted or unsubstituted C_{1-C6} alkyl, R_3 is substituted or unsubstituted phenyl, R_4 is hydrogen, L is hydrogen or substituted or unsubstituted C_{1-C6} alkyl, Q is O, S or NR_7, wherein R_7 is hydrogen or substituted or unsubstituted C_{1-C6} alkyl, and W is substituted or unsubstituted aryl.

118. The deazapurine of claim 117, wherein R_2 is --A--NHC(.dbd.O)B, wherein A and B are each independently unsubstituted C_{1-C4} alkyl.

119. The deazapurine of claim 118, wherein A is CH_{2CH2}.

120. The deazapurine of claim 118, wherein B is methyl.

121. The deazapurine of claim 118, wherein B is aminoalkyl.

122. The deazapurine of claim 121, wherein B is aminomethyl.

123. The deazapurine of claim 117, wherein R_3 is unsubstituted phenyl.

124. The deazapurine of claim 117, wherein L is hydrogen.

125. The deazapurine of claim 117, wherein R_6 is hydrogen or methyl.

126. The deazapurine of claim 125, wherein R_6 is hydrogen.

127. The deazapurine of claim 117, wherein Q is O.

128. The deazapurine of claim 117, wherein Q is S.

129. The deazapurine of claim 117, wherein Q is NR_7 wherein R_7 is hydrogen or substituted or unsubstituted C_{1-C6} alkyl.

130. The deazapurine of claim 129, wherein R_7 is hydrogen.

131. The deazapurine of claim 129, wherein R_7 is methyl.

132. The deazapurine of claim 117, wherein W is unsubstituted phenyl.

133. The deazapurine of claim 117, wherein W is phenyl with at least one substituent.

134. The deazapurine of claim 133, wherein said substituent is halogen.

135. The deazapurine of claim 134, wherein W is p-fluorophenyl.

136. The deazapurine of claim 134, wherein W is p-chlorophenyl.

137. The deazapurine of claim 133, wherein said substituent is alkoxy.

138. The deazapurine of claim 137, wherein W is p-methoxy.

139. The deazapurine of claim 117, wherein W is heteroaryl.

140. The deazapurine of claim 139, wherein W is 2-pyridyl.

141. The deazapurine of claim 117, wherein said deazapurine is 4-(2-acetylaminoethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

142. The deazapurine of claim 137, wherein said deazapurine is 4-(2-acetylaminoethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

143. The deazapurine of claim 117, wherein said deazapurine is 4-(2-acetylaminoethyl)amino-6-(4-chlorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

144. The deazapurine of claim 117, wherein said deazapurine is 4-2-acetylaminoethyl)amino-6-(4-methoxyphenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

145. The deazapurine of claim 117, wherein said deazapurine is 4-(2-acetylaminoethyl)amino-6-(2-pyridyloxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

146. The deazapurine of claim 117, wherein said deazapurine is 4-(2-acetylaminoethyl)amino-6-(N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

147. The deazapurine of claim 117, wherein said deazapurine is 4-(2-acetylaminoethyl)amino-6-(N-methyl-N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

148. The deazapurine of claim 117, wherein said deazapurine is 4-(2-N'-methylureaethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

149. A method for inhibiting the activity of an **adenosine receptor** in a cell, which comprises contacting said cell with a deazapurine of claims 11, 12, 14, 25, 63 or 65.

150. The method of claim 149, wherein said deazapurine is selected from the group consisting of: 4-(2-acetylaminoethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo [2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-chlorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-

methoxyphenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(2-pyridyloxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-methyl-N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-N'-methylureaethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(cis-3-hydroxycyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(cis-3-(2-aminoacetoxy)cyclopentyl)amino-5,6dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine trifluoroacetic acid salt, 4-(3-acetamido)piperidinyl-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-N''-methylureapropyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-acetamidobutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-N'-methylureabutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-aminocyclopropylacetamidoethyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(trans-4-hydroxycyclohexyl)amino-2-(3-chlorophenyl)-7H-pyrrolo[2,3d]pyrimidine, 4-(trans-4-hydroxycyclohexyl)amino-2-(3-fluorophenyl)-7H-pyrrolo[2,3d]pyrimidine, and 4-(trans-4-hydroxycyclohexyl)amino-2-(4-pyridyl)-7H-pyrrolo[2,3d]pyrimidine.

151. The method of claim 149, wherein said **adenosine receptor** is an A_{2b} **adenosine receptor**.

152. The method of claim 151, wherein said deazapurine is an **antagonist** of said A_{2b} **adenosine receptor**.

153. The method of claim 149, wherein said **adenosine receptor** comprises an A_3 **adenosine receptor**.

154. The method of claim 153, wherein said N-6 substituted 7-deazapurine is an **antagonist** of said A_3 **adenosine receptor**.

155. A method for treating a gastrointestinal disorder in an animal which comprises administering to said animal an effective amount of an deazapurine of claims 63 or 65.

156. The method of claim 155, wherein said deazapurine is selected from the group consisting of: 4-(2-acetylaminoethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-chlorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-methoxyphenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(2-pyridyloxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-methyl-N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; and 4-(2-N'-methylureaethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine.

157. The method of claim 155, wherein said disorder is diarrhea.

158. The method of claim 155, wherein said animal is a human.

159. The method of claim 155, wherein said deazapurine is an **antagonist** of A_{2b} **adenosine receptors** in cells of said animal.

160. A method for treating a respiratory disorder in an animal which comprises administering to said animal an effective amount of a deazapurine of claims 63 or 64.

161. The method of claim 160, wherein said deazapurine is selected from the group consisting of: 4-(2-acetylaminoethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-chlorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-methoxyphenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(2-pyridyloxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-methyl-N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; and 4-(2-N'-methylureaethyl)amino-6-phenoxymethyl-2-phenyl-7H-

pyrrolo[2,3d]pyrimidine.

162. The method of claim 160, wherein said disorder is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

163. The method of claim 160, wherein said animal is a human.

164. The method of claim 160, wherein said deazapurine is an **antagonist** of A_{2b} **adenosine receptors** in cells of said animal.

165. A method for treating a N-6 substituted 7-deazapurine responsive state in an animal, comprising administering to a mammal a therapeutically effective amount of a deazapurine of claim 11, 12, 14, 25, 63, or 64 such that treatment of a N-6 substituted 7-deazapurine responsive state in the animal occurs.

166. The method of claim 165, wherein said N-6 substituted 7-deazapurine responsive state is a disease state, wherein the disease state is a disorder mediated by adenosine.

167. The method of claim 166, wherein said disease state is a central nervous system disorder, a cardiovascular disorder, a renal disorder, an inflammatory disorder, an allergic disorder, a gastrointestinal disorder or a respiratory disorder.

168. A method for treating damage to the eye of an animal which comprises administering to said animal an effective amount of an N-6 substituted 7-deazapurine of claims 11, 12, 14 or 25.

169. The method of claim 168, wherein said N-6 substituted 7-deazapurine is selected from the group consisting of: 4-(cis-3-hydroxycyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(cis-3-(2-aminoacetoxy)cyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidinetrifluoroacetic acid salt, 4-(3-acetamido)piperidinyl-5,6-dimethyl-2-phenyl- 7H-pyrrolo[2,3d]pyrimidine, 4-(2-N'-methylureapropyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-acetamidobutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-N'-methylureabutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-aminocyclopropylacetamidoethyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(trans-4-hydroxycyclohexyl)amino-2-(3-chlorophenyl)-7H-pyrrolo[2,3d]pyrimidine, 4-(trans-4-hydroxycyclohexyl)amino-2-(3-fluorophenyl)-7H-pyrrolo[2;3d]pyrimidine, and 4-(trans-4-hydroxycyclohexyl)amino-2-(4-pyridyl)-7H-pyrrolo[2,3d]pyrimidine.

170. The method of claim 168, wherein said damage comprises retinal or optic nerve head damage.

171. The method of claim 168, wherein said damage is acute or chronic.

172. The method of claim 168, wherein said damage is the result of glaucoma, edema, ischemia, hypoxia or trauma.

173. The method of claim 168, wherein said animal is a human.

174. The method of claim 168, wherein said N-6 substituted 7-deazapurine is an **antagonist** of A_3 **adenosine receptors** in cells of said animal.

175. A pharmaceutical composition comprising a therapeutically effective amount of a deazapurine of claims 11, 12, 14, 25, 63 or 64 and a pharmaceutically acceptable carrier.

176. The pharmaceutical composition of claim 175, wherein said deazapurine is selected from the group consisting of: 4-(2-acetylaminoethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-chlorophenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(4-methoxyphenoxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(2-pyridyloxy)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-acetylaminoethyl)amino-6-(N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine;

4-(2-acetylamninoethyl)amino-6-(N-methyl-N-phenylamino)methyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(2-N'-methylureaethyl)amino-6-phenoxymethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine; 4-(cis-3-hydroxycyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(cis-3-(2-aminoacetoxy)cyclopentyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine trifluoroacetic acid salt, 4-(3-acetamido)piperidinyl-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-N'-methylureapropyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-acetamidobutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-N'-methylureabutyl)amino-5,6-dimethyl-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(2-aminocyclopropylacetamidoethyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine, 4-(trans-4-hydroxycyclohexyl)amino-2-(3-chlorophenyl)-7H-pyrrolo[2,3d]pyrimidine, 4-(trans-4-hydroxycyclohexyl)amino-2-(3-fluorophenyl)-7H-pyrrolo[2,3d]pyrimidine, and 4-(trans-4-hydroxycyclohexyl)amino-2-(4-pyridyl)-7H-pyrrolo[2,3d]pyrimidine.

177. The pharmaceutical composition of claim 175, wherein said therapeutically effective amount is effective to treat a respiratory disorder or a gastrointestinal disorder.

178. The pharmaceutical composition of claim 177, wherein said gastrointestinal disorder is diarrhea.

179. The pharmaceutical composition of claim 177, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

180. The pharmaceutical preparation of claim 175, wherein said pharmaceutical preparation is an ophthalmic formulation.

181. The pharmaceutical preparation of claim 180, wherein said pharmaceutical preparation is an periocular, retrobulbar or intraocular injection formulation.

182. The pharmaceutical preparation of claim 180, wherein said pharmaceutical preparation is a systemic formulation.

183. The pharmaceutical preparation of claim 180, wherein said pharmaceutical preparation is a surgical irrigating solution.

184. A packaged pharmaceutical composition for treating a N-6 substituted 7-deazapurine responsive state in a mammal, comprising: a container holding a therapeutically effective amount of at least one deazapurine of claims 11, 12, 14, 25, 63 or 64; and instructions for using said deazapurine for treating said N-6 substituted 7-deazapurine responsive state in a mammal.

185. A method for the preparation of ##STR185## comprising the steps of: a) reacting ##STR186## to provide ##STR187## wherein, P is a lower alkyl or a protecting group; b) cyclizing the product of step a) to provide ##STR188## c) chlorinating the product of step b) to provide ##STR189## and d) treating the product of step c) with an amine, thereby providing ##STR190## wherein R_1 and R_2 are each independently a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety or together form a substituted or unsubstituted heterocyclic ring; R_3 is a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; and R_5 is a halogen atom, a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety.

186. A method for the preparation of ##STR191## comprising the steps of: a) reacting ##STR192## to provide ##STR193## wherein P is a removable protecting group; b) treating the product of step a) under cyclization conditions to provide ##STR194## c) treating the product of step b) under suitable conditions to provide ##STR195## and d) treating the chlorinated product of step c) with an amine to provide ##STR196## wherein R_1 and R_2 are each independently a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylatyl moiety or together form a substituted or unsubstituted heterocyclic ring; R_3 is a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety; and R_6 is a halogen atom, a hydrogen atom or a substituted or unsubstituted alkyl, aryl, or alkylaryl moiety.

L14 ANSWER 28 OF 56 USPATFULL on STN
2002:4163 Method for identifying and using A2B **adenosine receptor antagonists** to mediate mammalian cell proliferation.
Belardinelli, Luiz, Menlo Park, CA, UNITED STATES
Grant, Maria B., Archer, FL, UNITED STATES
US 2002002142 A1 20020103
APPLICATION: US 2001-785895 A1 20010216 (9)
PRIORITY: US 2000-183141P 20000217 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method for inhibiting the proliferation of mammalian cells that express the A_{2B} **adenosine receptor** comprising administering a therapeutically effective amount of an A_{2B} **adenosine receptor antagonist** to the mammal.

2. The method of claim 1 wherein the cells that express the A_{2B} **adenosine receptor** are vascular endothelial cells.

3. The method of claim 2 wherein the vascular endothelial cells that express the A_{2B} **adenosine receptor** are selected from the group consisting of coronary endothelial cells, endothelial cells from the vascular bed.

4. The method of claim 3 wherein the vascular bed endothelial cells are selected from the group consisting of tumor endothelial cells, retinal endothelial cells, dermal endothelial cells, and brain endothelial cells.

5. The method of claim 1 wherein the endothelial cells are retinal endothelial cells.

6. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** inhibits the expression of vascular endothelial cell growth factor (VEGF).

7. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** is an A_{2B} **adenosine receptor** antisense oligonucleotide.

8. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** is an $A_{2B\text{-specific}}$ ribozyme.

9. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** is a non-selective **adenosine receptor antagonist**.

10. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** is a selective A_{2B} **adenosine receptor antagonist**.

11. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** is administered in an amount raging from about 1 microgram/kg to about 50 miligrams/kg.

12. The method of claim 1 wherein the adenosine A_{2B} **adenosine receptor antagonist** is administered in an amount ranging from about 1 microgram/kg to about 10 miligrams/kg.

13. The method of claim 1 wherein the A_{2B} **adenosine receptor antagonist** is administered by a method selected from the group consisting of orally, nasally, transdermally, by bolus, intravenously, in eye drops, by inhalation, and by using micropumps.

14. The method of claim 1 wherein the A_{2B} **adenosine receptor** agonist is administered in eye drops.

15. The method of claim 1 wherein the mammal is a human.

16. A method for assaying compounds to determine if they are A_{2B} **adenosine receptor antagonists** or A_{2B} **adenosine receptor** agonists comprising the steps of: a. preparing a first and second sample of human retinal endothelial cells; b. adding a compound to be tested to the first sample of human retinal endothelial cells and allowing the compound to remain in contact with the first sample of human retinal endothelial cells for a defmed period of time; and c.

comparing the number of new cells grown in the first sample with the number of new cells grown in the second sample.

17. An A_{2B} **adenosine receptor antagonist** compound identified by the method of claim 16 wherein the compound caused fewer new cells to grow in the first sample in comparison to the second sample.

18. An A_{2B} **adenosine receptor** agonist compound identified by the method of claim 16 wherein the compound caused more new cells to grow in the first sample in comparison to the second sample.

L14 ANSWER 29 OF 56 USPATFULL on STN
2001:178859 Method of culturing, cryopreserving and encapsulating pancreatic islet cells.
Opara, Emmanuel C., Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 6303355 B1 20011016
APPLICATION: US 1999-273407 19990322 (9)
DOCUMENT TYPE: Utility; GRANTED.

CLM What is claimed is:

1. A method of treating isolated pancreatic islet cells, comprising: (a) culturing said isolated pancreatic islet cells for from about 12 to about 36 hours in the presence of an antioxidant; then (b) cryopreserving said cells by freezing the cells in a cryopreservation medium comprising at least one compound selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic; then (c) thawing said cells, and (d) encapsulating said cells in a biocompatible microcapsule comprising a core and a semipermeable outer membrane, to provide a microcapsule containing living cells therein.

2. A method according to claim 1, wherein said cryopreservation medium contains at least two compounds selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

3. A method according to claim 1, wherein said cryopreservation medium contains at least three compounds selected from the group consisting of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

4. A method according to claim 1, wherein said cryopreservation medium contains at least one each of an antioxidant, an anti-cytokine, an anti-endotoxin, and an antibiotic.

5. A method according to claim 1, wherein said antioxidant is selected from the group consisting of glutathione, glutathione monoester, N-acetylcysteine, superoxide dismutase, catalase, vitamin E, α-tocopherol, lipoic acid, lazaroids, butylated hydroxyanisole (BHA), and vitamin K.

6. A method according to claim 1, wherein said anti-endotoxin is selected from the group consisting of L-N^G -Monomethylarginine (L-NMMA), lactoferrin, N-acetylcysteine (NAC), **adenosine receptor antagonists** and anti-lipopolysaccharide compounds.

7. A method according to claim 1, wherein said anti-cytokine is selected from the group consisting of dimethylthiourea, citiolone, pravastatin sodium; L-N^G -Monomethylarginine (L-NMMA), lactoferrin and 4-methylprednisolone.

8. A method according to claim 1, where said microcapsule comprises a polysaccharide gum surrounded by a semipermeable membrane.

9. A method according to claim 1 where said microcapsule comprises alginate and polylysine.

10. A method according to claim 1 wherein said microcapsule has an internal cell-containing core of alginate.

11. A method according to claim 10 wherein said internal cell-containing core of alginate is gelled.

12. A method according to claim 10 wherein said internal cell-containing core of alginate is not gelled.

13. A method according to claim 1 wherein said microcapsule has a diameter of from about 50 μm to about 2 mm.

14. A method according to claim 1 wherein said microcapsule has a diameter of from about 200 μm to about 1000 μm.

15. A method according to claim 1 wherein said microcapsule has a diameter of from about 300 μm to about 700 μm.

L14 ANSWER 30 OF 56 USPATFULL on STN
2001:171146 **Adenosine receptor** ligands and their use in the treatment of disease.
Borroni, Edilio Maurizio, Basle, Switzerland
Huber-Trottmann, Gerda, Grindel, Switzerland
Kilpatrick, Gavin John, England, Great Britain
Norcross, Roger David, Rheinfelden, Switzerland
US 2001027196 A1 20011004
APPLICATION: US 2001-788956 A1 20010220 (9)
PRIORITY: EP 2000-103432 20000225
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treatment of a disease state caused by malfunction of the **adenosine receptor** system comprising administering to a patient in need of such treatment, an effective amount of a composition for treating said disease state, said composition containing a compound that binds to an **adenosine receptor** and a pharmaceutically acceptable carrier, said compound having the formula: ##STR35## wherein A is selected from the group consisting of a bond, --S--, --N(R)--, $--(CH_2)_{2}--$, --CH.dbd.CH--, --C.tbd.C-- or --O--; X and Y each are independently selected from the group consisting of --N.dbd., .dbd.N--, --CH.dbd., .dbd.CH--, --C(cyano).dbd., .dbd.C(cyano)--, $--C[C(S)--NH_2].dbd.$, and $.dbd.C[C(S)-NH_2]--$, wherein at least one of X and Y is nitrogen; R^1 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, cyano, cycloalkyl, $--(CH_2)_{n}--C(O)O$-lower alkyl, $--(CH_2)_{n}--C(O)O$-lower alkyl-phenyl, $--(CH_2)_{n}--NH--C(O)O$-lower alkyl-phenyl, $--(CH_2)_{n}--O$-lower alkyl, $--(CH_2)_{n}--O$-phenyl, $--(CH_2)_{n}--NH$-phenyl, $--(CH_2)_{n}--$phenyl, $--(CH_2)_{n}$-phenyl substituted by 1 or 2 substituents selected from the group consisting of hydroxy, lower alkoxy, lower alkyl, CF_3-lower alkenyl, halogen, CF_3, OCF_3, and amino, $--(CH_2)_{n}$-N-di-lower alkyl, --C(O)NH-lower alkyl, $--S(O)_2$-lower alkyl, $--(CH_2)_{n}$-morpholinyl, $--(CH_2)_{n}$-amino, $--(CH_2)_{n}$-amino substituted by lower alkyl or benzyl, $--(CH_2)_{n}$-piperidin-1-yl or $--(CH_2)_{n}$-piperidin-3-yl, $--(CH_2)_{n}$-piperidin-1-yl or $--(CH_2)_{n}$-piperidin-3-yl, substituted by lower alkyl, $--(CH_2)_{n}$-pyridin-2-yl, $--(CH_2)_{n}$-pyridin-3-yl, $--(CH_2)_{n}$-pyridin-4-yl, $--(CH_2)_{n}$-pyridin-2-yl, $--(CH_2)_{n}$-pyridin-3-yl or $--(CH_2)_{n}$-pyridin-4-yl, substitutedtby 1 or 2 substituents, selected from lower alkyl, hydroxy, nitro, cyano, halogen, CF_3 or $--OC(O)N(R)_2$, $--(CH_2)_{n}--NH$-pyridin-2-yl, $--(CH_2)_{n}--NH$-pyridin-2-yl, substituted by lower alkyl, halogen, $--(CH_2)_{n}$-piperazin-4-yl, $--(CH_2)_{n}$-piperazin-4-yl, substituted by lower alkyl, phenyl or carbonyl-phenyl, $--(CH_2)_{n}$-phenyl-oc(O)-phenyl, $--(CH_2)_{n}$-phenyl--oc(O)-phenyl substituted by halogen, the group ##STR36## $--(CH_2)_{n}--S$-phenyl or $--(CH_2)_{n}--S(O)_2$-phenyl, $--(CH_2)_{n}--S$-lower alkyl, $--(CH_2)_{n}(CH.dbd.CH)_{m}$-phenyl, $--(CH_2)_{n}(CH.dbd.CH)_{m}$-phenyl, $--(CH_2)_{n}--NH$-cycloalkyl, $--(CH_2)_{n}--NH$-phenyl, $--(CH_2)_{n}--NH$-phenyl, substituted by amino or nitro, $--(CH_2)_{n}$-tetrahydro-pyran-4-yl, $--(CH_2)_{n}$-quinolin-2-yl, $--(CH_2)_{n}$-naphthyl or $--(CH_2)_{n}--NH$-naphthyl, $--(CH_2)_{n}$-3,4-dihydro-1H-isoquinolin-2-yl, $--(CH_2)_{n}$-benzo[1,3]dioxolyl, $--(CH_2)_{n}--NH--S(O)_2$-phenyl, $--(CH_2)_{n}--NH--S(O)_2$-phenyl substituted by halogen, $--(CH_2)_{n-1}$,2,3,4-tetrahydro-quinolin-2-yl, $--(CH_2)_{n-1}$,2,3,4-tetrahydro-quinolin-2-yl, substituted by lower alkyl or $--(CH_2)_{n}$-furanyl; R^2 is selected from the group consisting of hydrogen, halogen,

cyano, nitro, lower alkyl, lower alkenyl, --C(O)-lower alkyl, --C(O)O-lower alkyl, --C(O)O-lower alkyl-phenyl, lower alkynyl-phenyl, lower alkenyl--C(O)O-lower alkyl, lower alkenyl-cyano or phenyl, --C(O)O-lower alkyl, --C(O)O-lower alkyl-phenyl, lower alkynyl-phenyl, lower alkenyl-C(O)O-lower alkyl, lower alkenyl-cyano or phenyl, substituted by halogen; R^3 is selected from the group consisting of lower alkyl, phenyl, phenyl substituted by lower alkyl, lower alkoxy, or halogen, thien-2yl or fur-2yl, thien-2yl or fur-2yl, thien-2yl or fur-2yl, substituted by lower alkyl, S-lower alkyl, halogen, lower alkoxy, --C(O)O-lower alkyl, --C(.dbd.CH_2)--O-lower alkyl, --$(CH_2)_{n\text{-halogen}}$, --$(CH_2)_{n\text{--OH}}$, --$(CH_2)_{n}$-lower alkoxy, cyano, CHF_2, CH_{2F}, 2,3-dihydro-benzo[1.4]dioxin-6-yl, benzo[1.3]dioxol-5-yl, isoxazol-5-yl, pyridin-2-yl, pyridin-3-yl, --C(.dbd.CH_2)O-lower alkyl, 4,5-dihydrofuran-2-yl, 5,6-dihydro-4H-pyran-2-yl, oxazol-2-yl, benzofuranyl, pyrazin-2-yl, --O--$(CH_2)_{n\text{-phenyl}}$, --O--$(CH_2)_{n\text{-pyridyl}}$, --O--$(CH_2)_{n\text{-pyridyl}}$ substituted by lower alkyl, --S--$(CH_2)_{n\text{-pyridyl}}$, pyrazol-1-yl, pyrazol-1-yl substituted by lower alkyl or halogen; R^4 and R^5 are independently from each other selected from the group consisting of hydrogen, --CO--$(CH_2)_{n\text{--phenyl}}$, optionally substituted by halogen or --$CH_{2N}(R)(CH_2)_{n\text{-lower}}$ alkyl, phenyl, phenyl substituted by lower alkoxy, or --C(O)-phenyl; R is selected from the group consisting of hydrogen or lower alkyl; and A and R^2 may be together with the two carbon atoms ##STR37## and wherein n is , 1, 2, 3 or 4; m is 1 or 2; and pharmaceutically acceptable salts thereof.

2. The method of treatment of claim 1, wherein said compound has the structure of formula II ##STR38## wherein A, R^1 and R^3 are defined as in claim 1.

3. The method of treatment of claim 1 wherein said compound has the structure of formula III ##STR39## wherein A, R^1 and R^3 are as defined in claim 1.

4. The method of treatment of claim 1 wherein said compound has the structure of formula IV ##STR40## wherein A, R^1 and R^3 are as defined in claim 1.

5. The method of treatment of claim 1 using compounds of formula I wherein the disease state being treated includes Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure, substance abuse, sedation, said compounds serving as muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents.

6. The method of treatment of claim 1 wherein said treatment is based upon A_{2A} receptor **antagonistic** activity for the control or treatment of certain depressive disorders, neuroprotection and Parkinson's disease.

7. The method of treatment of claim 1 utilizing compounds of formula II ##STR41## wherein the substituents A, R^1 and R^3 are defined in claim 1.

8. The method of treatment of claim 1 utilizing compounds of formula III ##STR42## wherein the substituents A, R^1 and R^3 are defined in claim 1.

9. The method of treatment of claim I utilizing compounds of formula IV ##STR43## wherein the substituents A, R^1 and R^3 are defined in claim 1.

10. The method of treatment of claim 7 using compounds of formula II wherein A is --NH-- and R^1 and R^3 are as defined.

11. The use in accordance with claim 10, wherein the compounds are 2-Amino-4-benzylamino-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-propylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[2-(4-hydroxy-phenyl)-ethylamino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-phenylamino-ethylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-

phenylamino-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-phenoxy-ethylamino)-pyrimidine-5-carbonitrile, 2-amino-4-benzylamino-6-(5-methyl-furan-2-yl)-pyrimidine-5-carbonitrile, 6-furan-2-yl-5-nitro-N4-(3-phenyl-propyl)-pyrimidine-2,4-diamine, 2-amino-4-furan-2-yl-6-(2-methyl benzyamino)-pyrimidine-5carbonitrile, 2-amino-4-furan-2-yl-6-(3-methyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-methyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-methoxy-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-methyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(quinolin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(naphthalen-2-yl-methyl)-amino]-pyrmidine-5-carbonitrile, (RS)-2-amino-4-furan-2-yl-6-[(1,2,3,4-tetrahydro-quinolin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-phenylsulfanyl-ethylamino)-naphthalen-pyrimidine-5-carbonitrile, 2-amino-4-(2-amino-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-amino-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-dimethylamino-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-[2-(4-chloro-phenylamino)-ethylamino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-bromo-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[2-(pyridin-2-ylamino)-ethylamino]-pyrimidine-5-carbonitrile, 2-amino-4-[(benzo[1,3]dioxol-5-yl-methyl)-amino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-(3,4-dimethyl-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(4-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-(2-bromo-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(2-chloro-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(5-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(isoquinolin-3-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(3-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile 2-amino-4-furan-2-yl-6-(4-vinyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-(4-ethyl-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-3-chloro-5-trifluoromethyl-pyridin-2-yl-methyl)-amino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-[(3,5-dimethyl-pyridin-2-yl-methyl)-amino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4(4,5-dihydro-furan-2-yl)-6-[(4-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile or 2-amino-4-(2-bromo-benzylamino)-6-(5-bromo-furan-2-yl)-pyrimidine-5-carbonitrile.

12. The method of treatment of claim 10 for compounds of formula II as wherein A is --O-- and R^1 and R^3 are as defined in claim 1.

13. The use in accordance with claim 12, wherein the compounds are 2-amino-4-ethoxy-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-benzyloxy-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-phenethyloxy-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-propoxy)-pyrimidine-5-carbonitrile, 2-amino-4-cyclohexyloxy-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-isopropoxy-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-phenethyloxy-6-phenyl-pyrimidine-5-carbonitrile, 2-amino-4-phenyl-6-(pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(pyridin-2-yl-methoxy)-6-thiophen-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(pyridin-3-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(6-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-methyl-furan-2-yl)-6-(6-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-methyl-furan-2-yl)-6-(pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-allyloxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(naphthalen-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan -2-yl-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(5-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(isoquinolin-3-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(6-methyl-pyridin-3-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(3,5-dimethyl-pyridin-2-yl-methoxy)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(3-fluoro-phenyl)-6-(2-pyri din-2-yl -ethoxy) -pyrimidine-5-carbonitrile, 2-amino-4-(4-methyl-furan-2-yl)-6-(2-pyridin-2-yl -ethoxy) -pyrimidine

-5-carbonitrile, 2-amino-4-(5-methyl-furan-2-yl)-6-(3-methyl -pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(3,5-dimethyl-pyridin-2-ylmethoxy)-6-(5-methyl-furan-2-yl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(5-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(2-pyridin-2-yl-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(2-pyridin-2-yl-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-fran-2-yl)-6-(3,5-dimethyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(5-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(4-bromo-furan-2-yl)-6-(5-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, o 2-amino-4-(4-bromo-furan-2-yl)-6-(3,5-dimethyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile or 2-amino-4-(4-bromo-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile.

14. The method of treatmento of claim 10 for compounds of formula II, wherein A is --S-- and R^1 and R^3 are as defined in claim 1.

15. The method of treatment of claim 14, wherein the compounds are 2-Amino-4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-6-methylsulfanyl-. pyrimidine-5-carbonitrile, 2-amino-4-benzylsulfanyl-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-butylsulfanyl-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-ethylsulfanyl-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-phenyl-6-(3-phenyl-propylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-phenethylsulfanyl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-propylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(pyridin-2-yl-methylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(2-pyridin-2-yl-ethylsulfanyl)-6-thiophen-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-methyl-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yi)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-anino-4-(4-bromo-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-cyanomethyl-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(4-cyano-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile or 2-amino-4-(5-difluoromethyl-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile.

16. The method of treatment of claim 10 for compounds of formula II, wherein A is a bond and R^1 and R^3 are as defined in claim 1.

17. The method of treatment of claim 16, wherein the compounds are 2-Amino-4-furan-2-yl-6-piperidin-1-yl-pyrimidine-5-carbonitrile, 2-amino-6-furan-2-yl-pyrimidine-4,5-dicarbonitrile, 2-amino-4-furan-2-yl-6-phenyl-pyrimidine-5-carbontrile, (E)-2-amino-4-furan-2-yl-6-styryl-pyrimidine-5-carbonitrile or 2-amino-4-(3,4-dihydro-1H-isoquinolin-2-yl)-6-furan-2-yl-pyrimidine-5-carbonitrile.

18. The method of treatment of claim 8 for compounds of formula III wherein A is --NH--, --O-- or --S-- and R^1 and R^3 are as defined in claim 1.

19. The method of treatment of claim 18, wherein the compounds are 6-Amino-2-furan-2-yl-4-(pyridin-2-yl-methoxy)-nicotinonitrile, 6-amino-2-furan-2-yl-4-(2-pyridin-2-yl-ethylsulfanyl)-nicotinonitrile. 6-amino-2-furan-2-yl-4-(4-trifluoromethyl-benzylamino)-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(quinolin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl -4-[(pyridin-2-yl -methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(pyridin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(5-methyl-pyridin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-(3-methyl-pyridin-2-yl-methoxy)-nicotinonitrile or 6-amino-2-furan-2-yl-4-(2-pyridin-2-yl-ethoxy)-nicotinonitrile.

20. The method of treatment of claim 1 for compounds of formula I as defined in claim 1, wherein X and Y are nitrogen, A is --O--, --NH-- or --S--, R^2 is halogen or nitro and the other substituents are as defined in claim 1.

21. The use in accordance with claim 20, wherein the compound is 5-Bromo-4-furan-2-yl-6-(pyridin-2-yl-methoxy)-pyrimidin-2-yl-amine, 5-bromo-6-furan-2-yl-N4-(3-phenyl-propyl)-pyrimidine-2,4-diamine, 5-bromo-4-furan-2-yl-6-(3-phenyl-propoxy)-pyrimidin-2-yl-amine, 4-furan-2-yl-5-iodo-6-(3-phenyl-propoxy)-pyrimidin-2-yl-amine, 5-bromo-4-furan-2-yl-6-phenethylsulfanyl-pyrimidin-2-yl-amine, 5-bromo-4-furan-2-yl-6-(3-phenyl-allyloxy)-pyrimidin-2-yl-amine, 4-benzyloxy-6-furan-2-yl-5-nitro-pyrimidin-2-yl-amine, 5-chloro-6-furan-2-yl-N4-(3-phenyl-propyl)-pyrimidine-2,4-diamine, 5-chloro-4-furan-2-yl-6-(3-phenyl-propoxy)-py.midin-2-yl-amine, 5-chloro-4-furan-2-yl-6-phenethyloxy-pyrimidin-2-yl-amine, 4-benzylsulfanyl-5-chloro-6-furan-2-yl-pyrimidin-2-yl-amine, 4-furan-2-yl-S5-iodo-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl -amine, 5-bromo-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl-amine or 5-chloro-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl-amine.

22. The method of treatment of claim 1 for compounds of formula I, wherein X is .dbd.C(cyano)--, Y is --NH.dbd., A is --S-- and R^2 is CN and the other substituents are as defined in claim 1.

23. The method of treatment of claim 22, wherein the compound is 2-Amino-6-benzylsulfanyl-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile.

24. The method of treatment of claim 1 for compounds of formula I, wherein X and Y are nitrogen, A is --S--, R^2 is cyano and R is --C(O)-phenyl, and the other substituents are as defined in claim 1.

25. The method of treatment of claim 24, wherein the compound is N-[5-Cyano-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl]-benzamide.

26. A compound of formula ##STR44## wherein A is selected from the group consisting of a bond, --S--, --N(R)--, $--(CH_2)_{2}--$, --CH.dbd.CH--, --C--C-- or --O--; X and Y each are independently selected from the group consisting of --N.dbd., .dbd.N--, --CH.dbd., .dbd.CH--, --C(cyano).dbd., .dbd.C(cyano)--, $--C[C(S)-NH_2].dbd.$, and $.dbd.C[C(S)--NH_2]--$, wherein at least one of X or Y is nitrogen; R^1 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halogen, cyano, cycloalkyl, $--(CH_2)_{n}--C(O)O$-lower alkyl, $--(CH_2)_{n}--C(O)O$-lower alkyl-phenyl, $--(CH_2)_{n}--NH--C(O)O$-lower alkyl-phenyl, $--(CH_2)_{n}--O$-lower alkyl, $--(CH_2)_{n}--O$-phenyl, $--(CH_2)_{n}--NH$-phenyl, $--(CH_2)_{n}$-phenyl, $--(CH_2)_{n}$-phenyl substituted by 1 or 2 substituents selected from the group consisting of hydroxy, lower alkoxy, lower alkyl, CF_{3}-lower alkenyl, halogen, CF_3, OCF_3, and amino, $--(CH_2)_{n}$-N-di-lower alkyl, --C(O)NH-lower alkyl, $--S(O)_{2}$-lower alkyl, $--(CH_2)_{n}$-morpholinyl, $--(CH_2)_{n}$-amino, $--(CH_2)_{n}$-amino substituted by lower alkyl or benzyl, $--(CH_2)_{n}$-piperidin-1-yl or $--(CH_2)_{n}$-piperidin-3-yl, $--(CH_2)_{n}$-piperidin-1-yl or $--(CH_2)_{n}$-piperidin-3-yl, substituted by lower alkyl, $--(CH_2)_{n}$-pyridin-2-yl, $--(CH_2)_{n}$-pyridin-3-yl or $--(CH_2)_{n}$-pyridin-4-yl, $--(CH_2)_{n}$-pyridin-2-yl, $--(CH_2)_{n}$-pyridin-3-yl or $--(CH_2)_{n}$-pyridin-4-yl, substituted by 1 or 2 substituents, selected from lower alkyl, hydroxy, nitro, cyano, halogen, CF_3 or $--OC(O)N(R)_2$, $--(CH_2)_{n}--NH$-pyridin-2-yl, $--(CH_2)_{n}--NH$-pyridin-2-yl, substituted by lower alkyl, halogen, $--(CH_2)_{n}--$piperazin-4-yl, $--(CH_2)_{n}$-piperazin-4-yl, substituted by lower alkyl, phenyl or carbonyl-phenyl, $--(CH_2)_{n}$-phenyl-OC(O)-phenyl, $--(CH_2)_{n}$-phenyl-OC(O)-phenyl substituted by halogen, the group ##STR45## $--(CH_2)_{n}--S$-phenyl or $--(CH_2)_{n}--S(O)_{2}$-phenyl, $--(CH_2)_{n}--S$-lower alkyl, $--(CH_2)_{n}(CH.dbd.CH)_{m}$-phenyl, $--(CH_2)_{n}(CH.tbd.--CH)_{m}$-phenyl, $--(CH_2)_{n}--NH$-cycloalkyl, $--(CH_2)_{n}--NH$-phenyl, $--(CH_2)_{n}--NH$-phenyl, substituted by amino or nitro, $--(CH_2)_{n}--$tetrahydro-pyran-4-yl, $--(CH_2)_{n}$-quinolin-2-yl, $--(CH_2)_{n}$-quinolin-2-yl substituted by lower alkyl, $--(CH_2)_{n}--$naphthyl or $--(CH_2)_{n}--NH$-naphthyl, $--(CH_2)$-3,4-dihydro-1H-

isoquinolin-2-yl, --$(CH_2)_{n\text{-benzo}}$[1,3]dioxolyl, --$(CH_2)_{n}$--NH-$S(O)_{2\text{-phenyl}}$, --$(CH_2)_{n}$--NH-$S(O)_{2\text{-phenyl}}$ substituted by halogen, --$(CH_2)_{n\text{-}1}$,2,3,4-tetrahydro-quinolin-2-yl, --$(CH_2)_{n\text{-}1}$,2,3,4-tetrahydro-quinolin-2-yl, substituted by lower alkyl or --$(CH_2)_{n}$--furanyl; R^2 is selected from the group consisting of hydrogen, halogen, cyano, nitro, lower alkyl, lower alkenyl, --C(O)-lower alkyl, --C(O)O-lower alkyl, --C(O)O-lower alkyl-phenyl, lower alkynyl-phenyl, lower alkenyl--C(O)O-lower alkyl, lower alkenyl-cyano or phenyl, --C(O)O-lower alkyl, --C(O)O-lower alkyl-phenyl, lower alkynyl-phenyl, lower alkenyl--C(O)O-lower alkyl, lower alkenyl-cyano or phenyl, substituted by halogen; R^3 is selected from the group consisting of lower alkyl, phenyl, phenyl substituted by lower alkyl, lower alkoxy, or halogen, thien-2-yl or fur-2-yl, thien-2-yl or fur-2-yl, thien-2-yl or fur-2-yl, substituted by lower alkyl, S-lower alkyl, halogen, lower alkoxy, --C(O)O-lower alkyl, --C(.dbd.CH_2)--O-lower alkyl, --$(CH_2)_{n\text{-halogen}}$, --$(CH_2)_{n}$--OH, --$(CH_2)_{n}$-lower alkoxy, cyano, CHF_2, CH_2F, 2,3-dihydro-benzo[1.4]dioxin-6-yl, benzo[1,3]dioxol-5-yl, isoxazol-5-yl, pyridin-2-yl, pyridin-3-yl, --C(.dbd.CH_2)O-lower alkyl, 4,5-dihydrofuran-2-yl, 5 ,6-dihydro-4H-pyran-2-yl, oxazol-2-yl, benzofuranyl, pyrazin-2-yl, --O--$(CH_2)_{n\text{-phenyl}}$, --O--$(CH_2)_{n\text{-pyridyl}}$, --O--$(CH_2)_{n\text{-pyridyl}}$ substituted by lower alkyl, --S--$(CH_2)_{n\text{-pyridyl}}$, pyrazol-1-yl, pyrazol-1-yl substituted by lower alkyl or halogen; R^4 and R^5 are independently from each other selected from the group consisting of hydrogen, --CO--$(CH_2)_{n}$--phenyl, optionally substituted by halogen or --$CH_{2N}(R)(CH_2)_{n\text{-lower}}$ alkyl, phenyl, phenyl substituted by lower alkoxy, or --C(O)-phenyl; R is selected from the group consisting of hydrogen or lower alkyl; and A and R^2 may be together with the two carbon atoms ##STR46## and wherein n is 0, 1, 2, 3 or 4; m is 1 or 2; and pharmaceutically acceptable salts thereof.

27. The compound of claim 26 further comprising a compound having the structure of formula II wherein: ##STR47## A is --NH and R^1 and R^3 are as defined in claim 1.

28. The compound of claim 27 further comprising said compound having structure II wherein R^1 is selected from the group consisting of lower alkyl, cycloalkyl, --$(CH_2)_{n}$--phenyl, --$(CH_2)_{n\text{-phenyl}}$ substituted by 1 or 2 substituents selected from the group consisting of hydroxy, lower alkoxy, lower alkyl, $CF_{3\text{-lower}}$ alkenyl, halogen, CF_3, OCF_3, and amino, --$(CH_2)_{n\text{-pyridin-2-yl}}$, --$(CH_2)_{n\text{-pyridin-2-yl}}$, substituted by 1 or 2 substituents, selected from lower alkyl and CF_3, --$(CH_2)_{n}$(CH.dbd.CH)$_{m\text{-phenyl}}$, --$(CH_2)_{n}$--isoquinolin-3-yl, --$(CH_2)_{n}$--quinolin-2-yl, --$(CH_2)_{n\text{-naphthyl}}$, --$(CH_2)_{n}$-3,4-dihydro-1H-isoquinolin-2-yl, --$(CH_2)_{n}$--benzo[1,3]dioxolyl, --$(CH_2)_{n\text{-isoquinolin-3-yl}}$ --$(CH_2)_{n\text{-}1}$,2,3,4-tetrahydro-quinolin-2-yl, --$(CH_2)_{n\text{-}1}$,2,3,4-tetrahydro-quinolin-2-yl, substituted by lower alkyl; R^3 is selected from the group consisting of fur-2-yl, fur-2-yl, substituted by lower alkyl, and 4,5-dihydrofuran-2-yl; and wherein n is 0, 1, 2, 3 or 4; m is 1 or 2; and pharmaceutically acceptable salts thereof.

29. The compound of claim 28 further comprising compounds of formula II wherein A, R^1 and R^3 are as defined in claim 1, and wherein the compounds are: 2-Amino-4-benzylamino-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-propylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[2-(4-hydroxy-phenyl)-ethylamino]-pyrimidine-5-carbouitrile, 2-amino-4-furan-2-yl-6-(2-phenylarnino-ethylarnino)-pyrimidine-5-carbonitrile, 2-amino-4-fura-2-yl-6-[2-(4-methoxy-phenyl)-ethylamino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-phenylarnino-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-phenoxy-ethylamino)-pyrimidine-5-carbonitrile, 2-amino-4-benzylamino-6-(5-methyl-furan-2-yl)-pyrimidine-5-carbonitrile, 6-furan-2-yl-5-nitro-N4-(3-phenyl-propyl)-pyrimidine-2,4-diamine, 2-amino-4-furan-2-yl-6-(2-methyl -benzylamino)-pyrimidine-5-carbonitri le. 2-amino-4-furan-2-yl-6-(3-methyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-methyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-methoxy-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-methoxy-benzylamino)-pyrimidine-5-

carbonitrile, 2-amino-4-furan-2-yl-6-[(quinolin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(naphthalen-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, (RS)-2-amino-4-furan-2-yl-6-[(1;2,3,4-tetrahydro-quinolin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-phenylsulfanyl-ethylamino)-pyrimidine-5-carbonitrile, 2-amino-4-(2-amino-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-amino-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile. 2-amino-4-(4-dimethylamino-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-[2-(4-chloro-phenylamino)-ethylamino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-bromo-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[2-(pyridin-2-yl-amino)-ethylamino]-pyrimidine-5-carbonitrile, 2-amino-4-[(benzo[1,3]dioxol-5-yl-methyl)-amino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-trifluoromethyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-(3,4-dimethyl-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(4-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-(2-bromo-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(2-chloro-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(5-methyl-pyridin-2-ylmethyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(isoquinolin-3-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-[(3-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-vinyl-benzylamino)-pyrimidine-5-carbonitrile, 2-amino-4-(4-ethyl-benzylamino)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-[(3-chloro-5-trifluoromethyl-pyridin-2-yl-methyl)-amino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-[(3,5-dimethyl-pyridin-2-yl-methyl)-amino]-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4,5-dihydro-furan-2-yl)-6-[(4-methyl-pyridin-2-yl-methyl)-amino]-pyrimidine-5-carbonitrile or 2-amino-4-(2-bromo-benzylamino)-6-(5-bromo-furan-2-yl)-pyrimidine-5-carbonitrile; and the pharmaceutically acceptable salts thereof.

30. The compound of claim 26 further comprising a compound having the structure of formula II and the pharmaceutically acceptable salts thereof, wherein ##STR48## A is --O-- and R^1 and R^3 are as defined.

31. The compound of claim 30 further comprising said compound having the structure of formula II wherein R^1 is selected from the group consisting of lower alkyl, cycloalkyl, $--(CH_2)_{n\text{-phenyl}}$, $--(CH_2)_{n\text{-phenyl}}$ substituted by 1 or 2 substituents, selected from the group consisting of lower alkoxy, lower alkenyl, halogen, $--(CH_2)_{n\text{-pyridin-2-yl}}$, $--(CH_2)_{n\text{-pyridin-3-yl}}$, $--(CH_2)_{n\text{-pyridin-2-yl}}$, and $--(CH_2)_{n\text{-pyridin-3-yl}}$ substituted by 1 or 2 substituents, selected from lower alkyl, $--(CH_2)_n(CH.dbd.CH)_{m\text{-phenyl}}$, $--(CH_2)_n$-isoquinolin-3-yl, $--(CH_2)_{n\text{-naphthyl}}$; and wherein R^3 is selected from the group consisting of phenyl, phenyl substituted by halogen, thien-2-yl, fur-2-yl, thien-2-yl and fur-2-yl substituted by lower alkyl, and halogen; and wherein n is 0, 1, 2, 3 or 4; m is 1 or 2; and pharmaceutically acceptable salts thereof.

32. The compound of claim 31 further comprising compounds of formula II wherein A, R^1 and R^3 are as defined, and wherein the compounds are: 2-amino-4-ethoxy-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-benzyloxy-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-phenethyloxy-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-propoxy)-pyrimidine-5-carbonitrile, 2-amino-4-cyclohexyloxy-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-isopropoxy-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-phenethyloxy-6-phenyl-pyrimidine-5-carbonitrile, 2-amino-4-phenyl-6-(pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(pyridin-2-ylmethoxy)-6-thiophen-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(pyridin-, -yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(6-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-pyridin-2-yl-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-methyl-furan-2-yl)-6-(6-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-methyl-furan-2-yl)-6-(pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-allyloxy)-pyrimidine-5-carbonitnile, 2-amino-4-furan-2-yl-6-(naphthalen-2-yl-methoxy)-

pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitnile, 2-amino-4-furan-2-yl-6-(5-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(isoquinolin-3-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(4-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(6-methyl-pyridin-3-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(3,5-dimethyl-pyridin-2-yl-methoxy)-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(3-fluoro-phenyl-6-(2-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(4-metyl-furan-2yl)-6-(2-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-5-methyl-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile 2-amino-4-(3,5-dimethyl-pyridin-2-ylmethoxy)-6-(5-methyl-furan-2-yl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(5-methyl -pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(2-pyridin-2-yl-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(2-pyridin-2-yl-ethoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(3,5-dimethyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(5-methyl-pyridin-2-yl -methoxy)-pyrimidine-5-carbonitrile, 2-amino-4-(4-bromo-furan-2-yl)-6-(5-methyl-pyridin-2-yl-methoxy)-pyrimidin-5-carbonitrile, 2-amino-4-(4-bromo-furan-2-yl)-6-(3, 5-dimethyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile; 2-amino-4-(4-bromo-furan-2-yl)-6-(3-methyl-pyridin-2-yl-methoxy)-pyrimidine-5-carbonitrile; and the pharmaceutically acceptable salts thereof.

33. The compound of claim 26 further comprising a compound, and the pharmaceutically acceptable salts thereof, having the structure of formula II wherein: ##STR49## A is --S-- and R^1 and R^3 are as defined.

34. The compound of claim 33 further comprising said compound having the structure of formula II wherein R^1 is selected from the group consisting of lower alkyl, $--(CH_2)_{n\text{-phenyl}}$, $--(CH_2)_{n--\text{phenyl}}$ substituted by lower alkyl, $--(CH_2)_{n\text{-pyridin-2-yl}}$ substituted by lower alkyl; and wherein R^3 is selected from the group consisting of lower alkyl, thiene-2-yl, fur-2-yl, fur-2-yl substituted by halogen, $--(CH_2)_{n\text{-cyano}}$, CHF_2, and 2,3-dihydro-benzo[1.4]diosin-6-yl; and wherein n is 0, 1, 2, 3 or 4, m is 1 or 2.

35. The compound of claim 34 having the structure of formula II wherein the compounds are: 2-Amino-4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-6-methylsulfanyl-pyrimidine-5-carbonitrile 2-amino-4-benzylsulfanyl-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-butylsulfanyl-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-ethylsulfanyl-6-furan-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-phenyl-6-(3-phenyl-propylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-phenethylsulfanyl-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(3-phenyl-propylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(pyridin-2-yl-methylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(2-pyridin-2-yl-ethylsulfanyl)-6-thiophen-2-yl-pyrimidine-5-carbonitrile, 2-amino-4-(4-methyl-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-chloro-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-bromo-furan-2-yl)-6-(2-pyridin-2-yl -ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(4-bromo-furan-2-yl)-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(5-cyanomethyl-furan-2-yl)-6-(2-pyridin-2-yl -ethylsulfanyl)-pyrimidine-5-carbonitrile, 2-amino-4-(4-cyano-furan-2-yl)-6-(2-pyridin-2-yl-ethyl sulfanyl) -pyrimidine-5-carbonitrile or 2-amino-4-(5-difluoromethyl -furan-2-yl)-6-(2-pyridin-2-yl -ethylsulfanyl)-pyrimidine-5-carbonitrile.

36. The compound of claim 26 further comprising a compound, and the pharmaceutically acceptable salts thereof, having the structure of formula II wherein: ##STR50## A is a bond and R^1 and R^3 are as defined in claim 1.

37. The compound of claim 36 further comprising said compound having the I O structure of formula II wherein R^1 is selected from the group

consisting of cyano, --$(CH_2)_{n\text{-}phenyl}$, --$(CH_2)_n(CH.dbd.CH)_{m\text{-}phenyl}$, --$(CH_2)_{n\text{-}piperidin\text{-}1\text{-}yl}$, --$(CH_2)_{n\text{-}3,4\text{-}dihydro\text{-}1H\text{-}isoquinolin\text{-}2\text{-}yl}$; R^3 is -fur-2-yl; and wherein n=0 and m=1, and the pharmaceutically acceptable salts thereof.

38. The compound of claim 37 having the structure of formula II wherein the compounds are: 2-Amino-4-furan-2-yl-6-piperidin-1-yl-pyrimidine-5-carbonitrile, 2-amino-6-furan-2-yl-pyrimidine-4,5-dicarbonitrile, 2-amino-4-furan-2-yl-6-phenyl-pyrimidine-5-carbonitrile, (E)-2-amino-4-furan-2-yl-6-styryl-pyrimidine-5-carbonitrileor 2-amino-4-(3,4-dihydro-1H-isoquinolin-2-yl)-6-furan-2-yl-pyrimidine-5-carbonitrile; and the pharmaceutically acceptable salts thereof.

39. The compound of claim 26, and the pharmaceutically acceptable salts thereof, having the structure of formula III wherein: ##STR51## A is selected from the group consisting of --NH--, --O--, and --S-- and R^1 and R^3 are Us defined in claim 1.

40. The compound of claim 39 further comprising said compound having the structure of formula III wherein R^1 is selected from the group consisting of --$(CH_2)_{n\text{--}phenyl}$ substituted by CF3, --$(CH_2)_{n\text{-}pyridin\text{-}2\text{-}yl}$, substituted by lower alkyl, and --$(CH_2)_{n\text{-}quinolin\text{-}2\text{-}yl}$ substituted by lower alkyl, wherein n=0, 1, 2; R^3 is fur-2-yl and the pharmaceutically acceptable salts thereof.

41. The compound of claim 40 having the structure of formula III wherein the compounds are: 6-Amino-2-furan-2-yl-4-(pyridin-2-yl-methoxy)-nicotinonitrile, 6-amino-2-furan-2-yl-4-(2-pyridin-2-yl-ethylsulfanyl)-nicotinonitrile, 6-amino-2-furan-2-yl-4-(4-trifluoromethyl-benzylamino)-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(quinolin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(pyridin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(pyridin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-[(5-methyl-pyridin-2-yl-methyl)-amino]-nicotinonitrile, 6-amino-2-furan-2-yl-4-(3-methyl-pyridin-2-yl-methoxy)-nicotinonitrile, or 6-amino-2-furan-2-yl-4-(2-pyridin-2-yl-ethoxy)-nicotinonitrile, and the pharmaceutically acceptable salts thereof.

42. The compound of claim 26 having the structure of formula I further comprising A being selected from the group consisting of, O--, --NH--, --S--; R^2 being selected from the group consisting of halogen and nitro, and wherein R^1 is selected from the group consisting of --$(CH_2)_{n\text{--}phenyl}$ substituted lower alkoxy, lower alkyl, lower alkenyl, halogen, --$(CH_2)_{n\text{-}pyridin\text{-}2\text{-}yl}$ substituted by lower alkyl, and wherein R^3 is selected from the group consisting of fur-2-yl, and halogen substituted fur-2-yl; and the pharmaceutically acceptable salts thereof.

43. The compound of claim 42 having the structure of formula I wherein the compounds are: 5-Bromo-4-furan-2-yl-6-(pyridin-2-yl-methoxy)-pyrimidin-2-yl-amine, 5-bromo-6-furan-2-yl-N4-(3-phenyl-propyl)-pyrimidine-2,4-diamin, 5-bromo-4-furan-2-yl-6-(3-phenyl-propoxy)-pyrimidin-2-yl-amine, 4-furan-2-yl-5-iodo-6-(3-phenyl-propoxy)-pyrimidin-2-yl-amine, 5-bromo-4-furan-2-yl-6-phenethylsulfanyl-pyrimidin-2-yl-amine, 5-bromo-4-furan-2-yl-6-(3-phenyl-allyloxy)-pyrimidin-2-yl-amine, 4-benzyloxy-6-furan-2-yl-5-ntro-pyrimidin-2-yl-amine, 5-chloro-6-furan-2-yl-N4-(3-phenyl-propyl)-pyrimidine-2,4-diamine, 5-chloro-4-furan-2-yl-6-(3-phenyl-propoxy)-pyrimidin-2-yl-amine, 5-chloro-4-furan-2-yl-6-phenethyloxy-pyrimidin-2-yl-amine, 4-benzylsulfanyl-5-chloro-6-furan-2-yl-pyrimidin-2-yl-amine, 5-furan-2-yl-5-iodo-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl-amine, 5-brlomo-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl-amine or 5-chloro-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-pyrimidin-2-yl-amine; and the pharmaceutically acceptable salts thereof.

44. The compound of formula I as defined in claim 26, wherein X is .dbd.C(cyano)--, Y is --N.dbd., A is --S--, R^2 is CN and the compound is 2-Amino-6-benzylsulfanyl-4-thiophen-2-yl-pyridine-3,5-dicarbonitrile.

45. The compound of formula I as defined in claim 26, wherein X and Y are nitrogen, A is --S--, R^2 is cyano, R^5 is --C(O)-phenyl and the compound is N-[5-Cyano-4-furan-2-yl-6-(2-pyridin-2-yl-ethylsulfanyl)-

pyrimidin-2-yl}-benzamide.

L14 ANSWER 31 OF 56 USPATFULL on STN
2001:107877 Treatment of mental conditions including depression.
Renshaw, Perry F., Arlington, MA, United States
The McLean Hospital Corporation, Belmont, MA, United States (U.S. corporation)
US 6258794 B1 20010710
APPLICATION: US 2000-690286 20001017 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating a patient suffering from depression, said method comprising administering to said patient a pharmaceutical composition comprising (i) a compound that inhibits adenosine uptake or breakdown in vivo, or a compound that contains adenosine or an adenosine precursor, wherein the compound is processed in vivo to increase the circulating adenosine level in the patient; and (ii) a pharmaceutically acceptable carrier.

2. A therapeutic method for hypometabolic brain disorders comprising: (a) identifying a compound that inhibits adenosine uptake or breakdown in vivo or provides adenosine in vivo; (b) carrying out a diagnostic test to identify a patient suffering from a brain hypometabolic disorder associated with decreased brain adenosine levels; and (c) administering to said patient a pharmaceutical composition comprising said compound admixed with a pharmaceutically acceptable carrier.

3. The method of claim 2, wherein said patent suffers from depression, brain-affecting substance dependence, or a cerebral hypometabolic disorder.

4. The method of claim 3, wherein said depression is bipolar disorder or manic depression.

5. The method of claim 2, wherein said compound inhibits adenosine deaminase.

6. The method of claim 2, wherein said compound inhibits adenosine kinase.

7. The method of claim 6, wherein said adenosine kinase inhibitor is selected from the group consisting of 5'-amino-5'-deoxyadenosine, 5'-deoxy-5-iodotubercidin, 5'-iodotubericidin, iodotubericidin, 4-(N-phenylamino)-5-phenyl-7-(5'-deoxyribofuranosyl)pyrrolo[2,3-d]pyrimidine, and GP515.

8. The method of claim 2, wherein said compound is an **adenosine receptor antagonist**.

9. The method of claim 2, wherein the patient suffers from schizophrenia.

10. The method of claim 2, wherein the patient suffers from Huntington's Disease.

11. A therapeutic method comprising: (a) performing diagnostic testing on a patient to determine whether the patient is suffering from depression, brain-affecting substance dependence, or a cerebral hypometabolic disorder; and (b) if said diagnostic testing indicates that the patient is suffering from one of said disorders, administering to said patient an effective amount of a chemical compound selected from the group consisting of: (i) a compound that inhibits adenosine breakdown in vivo (ii) a compound that inhibits adenosine uptake in vivo (iii) a compound that contains adenosine or an adenosine precursor, wherein said compound is processed in vivo to increase the circulating adenosine level in said patient.

12. The method of claim 11, wherein the patient suffers from major depression and the compound inhibits adenosine uptake.

13. The method of claim 11, wherein the patient suffers from brain stimulant dependence and the compound inhibits adenosine uptake.

14. The method of claim 12, wherein the compound is EHNA.

15. The method of claim 12, wherein the compound is EHNA.

16. The method of claim 12, wherein said compound is propetofylline.

17. A diagnostic method for depression, said method comprising performing proton or phosphorous MRS resonance imaging on a human subject to measure the intensity of purine resonance and/or NTP resonance, wherein a lower than normal purine resonance intensity or NTP resonance intensity indicates depression.

18. The method of claim 17, wherein said lower intensity indicates depression that can be treated with a therapy that raises the level of circulating adenosine.

L14 ANSWER 32 OF 56 USPATFULL on STN
2001:48039 Methods and compositions for reducing ischemic injury of the heart by administering **adenosine receptor** agonists and **antagonists**.
Liang, Bruce T., Merion Station, PA, United States
Jacobson, Kenneth A., Silver Springs, MD, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US 6211165 B1 20010403
WO 9850047 19981112
APPLICATION: US 1999-423129 19991105 (9)
WO 1998-US9031 19980508 19991105 PCT 371 date 19991105 PCT 102(e) date
PRIORITY: US 1997-46030P 19970509 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for preventing or reducing ischemic damage to the heart, in a patient in need thereof, comprising administering to said patient an agonist having affinity for both the A1 and A3 **adenosine receptors** in an amount effective to activate A3 and A1 receptors in the heart of said patient.

2. A method as claimed in claim 1, wherein said agonist is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

3. A method as claimed in claim 1, wherein said agonist is selected from the group of compounds listed in Table II.

4. A method as claimed in claim 1, wherein said agonist is N^6-((2-trifluoromethyl)carbamoyl) adenosine-5'uronamide.

5. A method as claimed in claim 1, wherein said agonist is N^6-((3-iodophenyl)carbamoyl)adenosine-5'uronamide.

6. A method as claimed in claim 1 wherein said agonist is a binary conjugate which has affinity for, and activates the A1 and A3 **adenosine receptors** simultaneously.

7. A method as claimed in claim 1 wherein said agonist is administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

8. A method as claimed in claim 1, wherein said agonist is administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

9. A method as claimed in claim 1, wherein said agonist is administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

10. A method as claimed in claim 1, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, post myocardial infarction angina.

11. A method as claimed in claim 1, wherein said patient is in need of

such treatment due to acute myocardial infarction.

12. A method for preventing or reducing ischemic damage to the heart, in a patient in need thereof, comprising administering to said patient an mixed agonist having affinity for the A3 and A1 **adenosine receptors** and an **antagonist** having affinity for the A2a **adenosine receptor** in amounts effective to activate said A3 and A1 receptors and inhibit activation of said A2a receptor in the heart of said patient.

13. A method as claimed in claim 12, wherein said agonist and said **antagonist** are delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

14. A method as claimed in claim 12, wherein said agonist is selected from the group consisting of N^6 -((3-iodophenyl)carbamoyl)adenosine-5'uronamide, N^6 -((2-trifluoromethyl)carbamoyl)adenosine-5'uronamide, N^6 -(4-nitrobenzyl)adenosine-5'-N-ethyluronamide, 6-(O-henylhydroxylamino purine-9-beta-ribofuranoside-5'-N-methyluronamide, N^6 -cyclohexyl-5'-N-ethylcarboxamido)adensine, and N^6 -[4-[[[4-[2-aminoethyl)amino]carbonyl]methyl]-anilino]carbonyl]methyl]phenyl]adenosine.

15. A method as claimed in claim 12 wherein said **antagonist** is selected from the group of 8 styrylxanthine derivative compounds listed in Table III consisting of compounds 15b, 17b, 19b, 20b, 21b, 22b, 23, 24, 25, 26, 27b, 28, 29b, 32b, 33a, 33b, 34b, 35, 36, 37, 38, 39, 40, 41, 42, 43b, 44b, 45b, 46, 51b, 52b, 53b.

16. A method as claimed in claim 12, wherein said agonist is N^6 -((2-trifluoromethyl)carbamoyl)adenosine-5'uronamide.

17. A method as claimed in claim 12, wherein said agonist is N^6 -((3-iodophenyl)carbamoyl)adenosine-5'uronamide.

18. A method as claimed in claim 12, wherein said agonist is selected from the group consisting of MRS 584, MRS 479, MRS 537 or MRS 1340.

19. A method as claimed in claim 12, wherein said **antagonist** is selected from the group consisting of CSC, DMPX, ZM241385 or SCH58261.

20. A method as claimed in claim 12, wherein said agonist and said **antagonist** are administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

21. A method as claimed in claim 12, wherein said agonist and said **antagonist** are administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

22. A method as claimed in claim 12, wherein said agonist and said **antagonist** are administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

23. A method as claimed in claim 12, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

24. A method as claimed in claim 12, wherein said patient is in need of said treatment due to acute myocardial infarction.

25. A method for preventing or reducing ischemic damage to the heart, in a patient in need thereof, comprising administering to said patient a binary conjugate, which acts as an adenosine A3 receptor agonist while simultaneously inhibiting the activation of A2a receptors in an amount effective to enhance myocardial response to said preconditioning stimuli.

26. A method as claimed in claim 25, wherein said patient is in need of such treatment due to a cardiac condition selected from the group consisting of chronic stable angina, unstable angina, post-myocardial infarction angina or acute myocardial infarction.

27. A method as claimed in claim 25 wherein said agonist is administered to said patient prior to a surgical procedure which may cause cardiac

ischemic damage.

28. A method as claimed in claim 25, wherein said agonist is administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

29. A method as claimed in claim 25, wherein said agonist is administered to said patient following a surgical procedure which may result in cardiac ischemic damage.

30. A method for preventing or reducing ischemic damage to the heart, in a patient in need thereof, comprising administering to said patient both an adenosine A3 receptor agonist and at least one adenosine A1 receptor agonist in an amount effective to activate the A1 and A3 **adenosine receptors** in the heart of said patient.

31. A method as claimed in claim 30, wherein said agonists are delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

32. A method as claimed in claim 30, wherein said agonist and said agonists are administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

33. A method as claimed in claim 30, wherein said agonist and said **antagonist** are administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

34. A method as claimed in claim 30, wherein said agonist and said **antagonist** are administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

35. A method as claimed in claim 30, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

36. A method as claimed in claim 30, wherein said patient is in need of said treatment due to acute myocardial infarction.

37. A method as claimed in claim 30, wherein said A3 agonist is selected from the group of compounds consisting of IB-MECA, Cl-IB-MECA, MRS 584, MRS 479, MRS 537, MRS 1340, and DBXMR and said A1 agonist is selected from the group of compounds listed in Table I consisting of CPA, CCPA, ADAC R-PIA, SPA, CHA, SDZWAG 994 and NNC21-0136.

38. A binary conjugate for preventing or reducing ischemic damage to the heart, said conjugate acting as an agonist at the A3 **adenosine receptor** and an **antagonist** at the A2a **adenosine receptor**.

39. A binary conjugate as claimed in claim 38, said conjugate having the structure of MRS 1528.

40. A method for administering the binary conjugated of claim 38, wherein said conjugate is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

41. A method as claimed in claim 40, wherein said conjugate is administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

42. A method as claimed in claim 40, wherein said conjugate is administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

43. A method as claimed in claim 40, wherein said conjugate is administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

44. A method as claimed in claim 40, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

45. A method as claimed in claim 40, wherein said patient is in need of said treatment due to acute myocardial infarction.

46. A binary conjugate for preventing or reducing ischemic damage to the heart, said conjugate acting as an agonist at the A3 **adenosine receptor** and an agonist at the A1 **adenosine receptor**.

47. A binary conjugate as claimed in claim 46, said conjugate being selected from the group of compounds consisting of i) MRS1543, ii) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-glycyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, iii) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-alanyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, iv) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-methionyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, v) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-valyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, vi) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-leucyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, vii) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-isoleucyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenos viii) a conjugate of N^6 -[4-[[[4-(carboxymethyl)anilino]anilino]carbonyl]methyl]phenyl]adenosine and L-phenylalanyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine.

48. A binary conjugate as claimed in claim 46, said conjugate being selected from the group of compounds consisting of i) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and L-glycyl-N^6 -3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, ii) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and L-alanyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, iii) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and Ch_3]L-methionyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, iv) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and L-valyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, v) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and L-leucyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, vi) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and L-isoleucyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine, vii) a conjugate of N^6 -[4-(carboxymethyl)phenyl]adenosine and L-phenylalanyl-N^6 -[3-(3-amino-1-propynyl)benzyl]-5'-N-methylcarboxamidoadenosine.

49. A method for administering the binary conjugated of claim 46, wherein said conjugate is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

50. A method as claimed in claim 49, wherein said conjugate is administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

51. A method as claimed in claim 49, wherein said conjugate is administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

52. A method as claimed in claim 49, wherein said conjugate is administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

53. A method as claimed in claim 49, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

54. A method as claimed in claim 49, wherein said patient is in need of said treatment due to acute myocardial infarction.

55. A recombinant cardiac myocyte comprising nucleic acid molecules encoding two or more **adenosine receptors** selected from the group consisting of the A1 receptor, the A3 receptor, and the A2a receptor.

56. A recombinant myocyte as claimed in claim 55, whrerein the myocyte is a chick embryo ventricular myocyte and the **adenosine receptor** is a human **adenosine receptor**.

57. A method for determining whether a test compound exerts a cardioprotective effect, comprising: a) providing a recombinant myocyte expressing an **adenosine receptor** as claimed in claim 55; b) contacting said cells with said test compound; c) exposing cells to ischemic conditions; and d) assessing the presence of said cardioprotective effect, if any, exerted by said test compound.

58. A method as claimed in claim 57, wherein said cardioprotective effect is assessed by determining the number of myocytes killed.

59. A method as claimed in claim 57, wherein said cardioprotective effect is assessed by determining the amount of creatine kinase released from said recombinant cardiac myocytes.

60. A method as claimed in claim 57, wherein said recombinant myocyte is selected from the group consisting of chick embryo ventricular myocytes or adult rat ventricular myocytes.

L14 ANSWER 33 OF 56 USPATFULL on STN
2000:167749 Method and compositions for treating and diagnosing tumors using **adenosine receptor** activated cells.
Neely, Constance, Raleigh, NC, United States
Link Technology Incorporated, Raleigh, NC, United States (U.S. corporation)
US 6159701 20001212
APPLICATION: US 1996-748559 19961108 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of imaging tumor cells in vivo in a subject, comprising: (a) obtaining a sample of treatment cells from a subject, said treatment cells selected from the group consisting of macrophages, monocytes and splenocytes; (b) priming said treatment cells by contact with a priming agent in an amount sufficient to prime said treatment cells; (c) labeling said treatment cells with a radiolabelled A1 adenosine receptor agonist, said A1 **adenosine receptor** agonist provided in an amount sufficient and for a time sufficient to induce cytotoxicity in said treatment cells; and then (d) administering said labelled treatment cells to the subject in an amount effective to provide a radioimage of tumor cells present in said subject.

2. The method of claim 1 wherein said selective A_1 **adenosine receptor** ligand is a selective A_1 **adenosine receptor** agonist in an amount sufficient to induce cytotoxicity in said treatment cells.

3. The method of claim 1 wherein said treatment cells are monocytes, and said monocytes are cultured to provide macrophages for priming in step (b).

4. The method of claim 1 wherein said priming agent is selected from the group consisting of phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon gamma (IFNτ), granulocyte-macrophage colony stimulating factor (GMCSF), and f-met-leu-phe (FMLP).

5. The method of claim 1 wherein said subject is human.

6. The method of claim 1 further comprising contacting said treatment cells to an allosteric enhancer in an amount effective to enhance the binding of A_1 **adenosine receptor** agonists to A_1 **adenosine receptors**.

7. The method of claim 1 further comprising contacting said treatment cells to dexamethasone in an amount effective to increase the number of A_1 **adenosine receptor** receptors on said treatment cells.

8. The method of claim 1 further comprising contacting said treatment

cells to a protein kinase inhibitor.

9. The method of claim 1 further comprising the step of contacting said treatment cells to an A_2 **adenosine receptor antagonist**.

10. The method of claim 1 further comprising, prior to step (b), subjecting said treatment cells to a period of hypoxia and re-oxygenation sufficient to increase A_1 **adenosine receptor** activity.

11. The method of claim 1 wherein said administering step is carried out by administering said labelled treatment cells systemically to the subject.

12. The method of claim 1 wherein said administering step is carried out by administering said labelled treatment cells directly to tissue suspected of containing tumor cells.

L14 ANSWER 34 OF 56 USPATFULL on STN
2000:121089 Methods for the prevention and treatment of fibrosis and sclerosis.
Neely, Constance F., Raleigh, NC, United States
Link Technology Inc., Research Triangle Park, NC, United States (U.S. corporation)
US 6117445 20000912
APPLICATION: US 1998-224534 19981231 (9)
PRIORITY: US 1998-72896P 19980128 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating a disorder that results in fibrosis or sclerosis, in a subject in need of such treatment, comprising administering to said subject a composition selected from the group consisting of: (a) A_1 **adenosine receptor antagonists**; (b) P_{2X} purinoceptor **antagonists**; and (c) a combination of at least one A_1 **adenosine receptor antagonist** and at least one P_{2X} purinoceptor **antagonist**; wherein said composition is administered in an amount effective to reduce the rate of fibrosis or sclerosis.

2. The method of claim 1 wherein said disorder is selected from skeletal muscle fibrosis, irradiation-induced fibrosis, autoimmune-related fibrosis, cardiovascular fibrosis, arteriosclerotic disorders, pulmonary fibrosis, adult respiratory distress syndrome, inflammatory disorders, scleroderma, cirrhosis, keloids, adhesions and hypertrophic scars.

3. A method of claim 1 wherein said disorder is skeletal muscle fibrosis associated with a condition selected from muscular dystrophy, denervation atrophy induced by neuromuscular disease, and traumatic injury-induced denervation atrophy.

4. A method according to claim 1 wherein said disorder is cardiovascular fibrosis selected from left ventricular hypertrophy secondary to hypertension, fibrosis associated with myocardial infarction, fibrosis associated with ischemiareperfusion injury, and fibrosis associated with myocarditis.

5. A method according to claim 1, wherein said disorder is a dermal fibrosis.

6. A method according to claim 1,wherein said disorder is selected from keloid formation, hypertrophic scar formation, or adhesion formation.

7. A method according to claim 1, wherein said disorder is an ophthalmic fibrosis.

8. A method according to claim 1, wherein said composition is administered topically.

9. A method according to claim 1, wherein said composition is administered parenterally.

10. A method according to claim 1, wherein said disorder is a dermal fibrosis and said composition is administered topically.

11. A method according to claim 1, wherein said disorder is pulmonary fibrosis and said composition is administered by inhalation.

12. A method according to claim 1, wherein said disorder is rheumatoid arthritis and said composition is administered by intra-articular injection.

13. A method according to claim 1, wherein said composition is administered directly to the affected anatomic site.

14. A method according to claim 1, wherein said composition is administered prophylactically.

15. A method according to claim 1, wherein said A_1 **adenosine receptor antagonist** is an antibody that binds to the A_1 **adenosine receptor**.

16. A method according to claim 1, wherein said P_{2X} purinoceptor **antagonist** is an antibody that binds to the P_{2X} purinoceptor.

17. A method of preventing fibrosis or sclerosis in a subject in need of such treatment, comprising administering to said subject a composition selected from the group consisting of: (a) A_1 **adenosine receptor antagonists**; (b) P_{2X} purinoceptor **antagonists**; and (c) a combination of at least one A_1 **adenosine receptor antagonist** and at least one P_{2X} purinoceptor **antagonist**; wherein said composition is administered in an amount effective to reduce the formation of fibrotic or sclerotic tissue that would occur in the absence of such treatment.

18. A method according to claim 17, wherein said fibrosis or sclerosis is due to keloid formation, hypertrophic scar formation, or adhesion formation.

19. A method according to claim 17, wherein said fibrosis is pulmonary fibrosis.

20. A method according to claim 19, wherein said pulmonary fibrosis is due to adult respiratory distress syndrome or irradiation induced fibrosis.

21. A method according to claim 17, wherein said composition is administered prior to scheduled surgery.

22. A method according to claim 17, wherein said A_1 **adenosine receptor antagonist** is an antibody that binds to the A_1 **adenosine receptor**.

23. A method according to claim 17, wherein said P_{2X} purinoceptor **antagonist** is an antibody that binds to the P_{2X} purinoceptor.

L14 ANSWER 35 OF 56 USPATFULL on STN
2000:57775 Method for improving insulin sensitivity using an **adenosine receptor antagonist**.
LaNoue, Kathryn F., Hershey, PA, United States
Crist, George H., Harrisburg, PA, United States
Linden, Joel M., Charlottesville, VA, United States
The Penn State Research Foundation, University Park, PA, United States (U.S. corporation)
US 6060481 20000509
APPLICATION: US 1999-259201 19990301 (9)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for improving insulin sensitivity in a patient comprising: administering to said patient an effective amount of at least one A_{2B} **adenosine receptor antagonist**, or a pharmaceutically acceptable salt or solvate thereof.

2. The method of claim 1, wherein said patient has non-insulin dependent diabetes mellitus.

3. The method of claim 1, wherein said patient is pre-diabetic.

4. The method of claim 1, wherein said patient has impaired glucose tolerance.

5. The method of claim 1, wherein said A_{2B} **adenosine receptor antagonist**, salt or solvate thereof is contained in a suitable pharmaceutical carrier.

6. The method of claim 5, wherein said suitable pharmaceutical carrier is selected from the group comprising a liquid carrier and a solid carrier.

7. The method of claim 1, wherein said method of administration is oral, parenteral or rectal.

8. The method of claim 7, wherein administration is oral.

9. The method of claim 1, wherein said effective amount of said **antagonist** is enough to achieve blood concentrations of at least ten times the binding constant for the **antagonist**.

10. The method of claim 1, wherein said A_{2B} **adenosine receptor antagonist** is a xanthine derivative.

11. The method of claim 10, wherein said xanthine derivative is selected from the group comprising 3-n-propylxanthine, 1,3-dipropyl-8-(p-acrylic)phenylxanthine, 1,3-dipropyl-8-cyclopentylxanthine, 1,3-dipropyl-8-p-sulfophenyl)xanthine, xanthine amine congener, and 1,3-dipropyl-8-[2-(5,6-epoxynorbonyl] xanthine.

12. The method of claim 10, wherein said xanthine derivative is 1,3-dimethylcyclohexyl-8-phenyl(4-acrylate)-xanthine.

13. A method for stimulating glucose uptake in the muscle of a patient comprising: administering to said patient an effective amount of at least one A_{2B} **adenosine receptor antagonist**, or a pharmaceutically acceptable salt or solvate thereof.

14. The method of claim 13, wherein said A_{2B} **adenosine receptor antagonist**, salt or solvate thereof is contained in a suitable pharmaceutical carrier.

15. The method of claim 13, wherein said A_{2B} **adenosine receptor antagonist** is a xanthine derivative.

L14 ANSWER 36 OF 56 USPATFULL on STN
1999:163697 Compositions and methods for use in ischemia-reperfusion and endotoxin-related tissue injury.
Neely, Constance F., Raleigh, NC, United States
Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 6001842 19991214
APPLICATION: US 1998-4938 19980109 (9)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of preventing or treating endotoxin-related tissue injury in an animal comprising administering to an animal an effective amount of an A_1 **adenosine receptor antagonist** so that endotoxin-related tissue injury is prevented or treated.

2. The method of claim 1 further comprising administering an effective amount of a P_{2X} purinoceptor **antagonist**.

3. The method of claim 1 further comprising administering to the animal an antibiotic, steroid, or anti-inflammatory treatment used in the treatment of endotoxin-related tissue injury.

4. The method of claim 2 further comprising administering to the animal an antibiotic, steroid, or anti-inflammatory treatment used in the treatment of endotoxin-related tissue injury.

5. A method of preventing or treating endotoxin-related tissue injury in an animal comprising administering to an animal an effective amount of a

P_{2x} purinoceptor **antagonist** so that endotoxin-related tissue injury is prevented or treated.

6. The method of claim 5 further comprising administering to the animal an antibiotic, steroid, or anti- inflammatory treatment.

L14 ANSWER 37 OF 56 USPATFULL on STN
1999:160039 Methods for modulating melanin production.
Manneth, Victor, Sunnyvale, CA, United States
Patel, Rajesh, Redwood City, CA, United States
Therasys, Inc., Redwood City, CA, United States (U.S. corporation)
US 5998423 19991207
APPLICATION: US 1997-940338 19970930 (8)
PRIORITY: US 1996-27944P 19961008 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of modulating melanin production in the skin or hair comprising applying to said skin or hair, an effective amount of a melanin production modulating agent selected from the group consisting of an adenosine-1 receptor **antagonist**, an adenosine-2 receptor agonist, an adenosine-1 receptor agonist, an adenosine-2 receptor **antagonist** and a combination of an adenosine-1 receptor **antagonist** and adenosine-2 receptor agonist or of an adenosine-1 receptor agonist and an adenosine-2 receptor **antagonist**, in a pharmaceutically acceptable lotion or cream.

2. A method in accordance with claim 1, wherein said modulation is an increase in melanin production and said compound is an adenosine-1 receptor **antagonist**.

3. A method in accordance with claim 2, wherein said adenosine-1 receptor **antagonist** is a triazoloquinoline.

4. A method in accordance with claim 2, wherein said adenosine-1 receptor **antagonist** is a triazoloquinoxaline.

5. A method in accordance with claim 4, wherein said triazoloquinoxaline has the structure ##STR1## .

6. A method in accordance with claim 2, wherein said adenosine-1 receptor **antagonist** is an imidazoquinoline.

7. A method in accordance with claim 2, wherein said adenosine-1 receptor **antagonist** is a pyrrolo[2,3-d]pyrimidine.

8. A method in accordance with claim 7, wherein said pyrrolo[2,3-d]pyrimidine is 2-phenyl-7-deazaadenine.

9. A method in accordance with claim 2, wherein said adenosine-1 receptor **antagonist** is a N^6 -substituted-9-menthyladenine.

10. A method in accordance with claim 9, wherein said N^6 -substituted-9-methyladenine has the structure ##STR2## wherein R is cyclopentyl, cyclohexyl or norbornyl.

11. A method in accordance with claim 2, wherein said adenosine-1 receptor **antagonist** is a cycloalkylxanthine and phenylxanthine.

12. A method in accordance with claim 11, wherein said cycloalkylxanthine is a 1,3-dimethyl-8-cyclopentylxanthine or a 1,3-dipropyl-8-cyclopentylxanthine.

13. A method in accordance with claim 1, wherein said modulation is an increase in melanin production and said compound is an adenosine-2 receptor agonist.

14. A method in accordance with claim 13, wherein said adenosine-2 receptor agonist is a member selected from the group consisting of imidazo[4,5-b]pyridines, N^9 -cyclopentyl-substituted adenine derivatives and 2-(p-(2-carboxyethyl)phenethylamino)-5'-N-ethylcarboxamidoadenosine.

15. A method in accordance with claim 13, wherein said adenosine-2

receptor agonist is a member selected from the group consisting of 2-((cyclohexylethyl)-amino)adenosine, 2-((cyclohexenylethyl)amino)adenosine, 2-((cyclohexylethoxy)adenosine, and 2-(carboxyethyl(phenylethyl)amino)adenosine.

16. A method in accordance with claim 1, wherein said modulation is a decrease in melanin production and said compound is an adenosine-1 receptor agonist.

17. A method in accordance with claim 16, wherein said adenosine-1 receptor agonist is a member selected from the group consisting of 1-deaza-2-chloro-N -cyclopentyl-adenosine, N^6 -cyclopentyladenosine, N^6 -cyclohexyladenosine, 2-chloro-N^6 -cyclopentyladenosine and R-N^6 -(2-phenyl-1 -methylethyl)adenosine.

18. A method in accordance with claim 1, wherein said modulation is a decrease in melanin production and said compound is an adenosine-2 receptor **antagonist**.

19. A method in accordance with claim 18, wherein said adenosine-2 receptor **antagonist** is a member selected from the group consisting of 1-acetylene-3-methylxanthine, 5'-deoxy-5'-methylthioadenosine, 2-chloro-5'-deoxy-5'-methylthioadenosine, 5'-deoxy-5'-iodoadenosine, adenosine-5'-O-ethylcarbonate, and 5'-O-nitroadenosine.

20. A method in accordance with claim 18, wherein said **adenosine-receptor antagonist** is a member selected from the group consisting of 9-chloro-2-(2-furyl)--[1,2,4]triazolo-[1,5-c]quinazolin-5-amine, 4-amino-8-chloro-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline, and 3-(3-hydroxyphenyl)5H-thiazolo[2,3-b]quinazoline.

L14 ANSWER 38 OF 56 USPATFULL on STN

1999:4676 Methods for protecting against cardiac ischemia by administering adenosine A_{2a} receptor **antagonists**.

Liang, Bruce T., Merion Station, PA, United States
Jacobson, Kenneth A., Silver Spring, MD, United States
Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)National Institute of Health, Rockville, MD, United States (U.S. corporation)
US 5859019 19990112
APPLICATION: US 1997-813787 19970307 (8)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A method for preventing or reducing ischemic damage to heart muscle cells in a patient in need of such treatment or at risk for said ischemic damage, comprising administering to said patient an **antagonist** to an A2a receptor in an amount effective to inhibit A2a receptor activation in the heart of said patient without activation of an A3 **adenosine receptor**.

2. A method as claimed in claim 1, wherein said **antagonist** is administered intravenously.

3. A method as claimed in claim 1, wherein said **antagonist** is administered by cardiac perfusion.

4. A method as claimed in claim 1, wherein said **antagonist** is administered orally.

5. A method as claimed in claim 1, wherein said **antagonist** is a compound selected from the group consisting of 1,3,7-trimethyl-8-styrylxanthine, 1,3,7-trimethyl-8-(2-methoxystyryl)xanthine, 1,3,7-trimethyl-8-(3-methoxystyryl)xanthine, 1,3,7-trimethyl-8-[3-(trifluoromethyl)styryl]xanthine, 1,3,7-trimethyl-8-(3-nitrostyryl)xanthine, 1,3,7-trimethyl-8-(3-aminostyryl)xanthine, 1,3,7-trimethyl-8-[3-(acetylamino)styryl]xanthine, 1,3,7-trimethyl-8-[3-[3(-carboxyl-1-oxopropyl)amino]-styryl]xanthine, 1,3,7-trimethyl-8-[3-[(tert-butyloxy)carbonyl]amino]-styryl]xanthine, 1,3,7-trimethyl-8-[3-[bis[(tert-butyloxy)carbonyl]amino]-styryl]xanthine, 1,3,7-trimethyl-8-(3-fluorostyryl)xanthine, 1,3,7-trimethyl-8-(4-methoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,4-dimethoxystyryl)xanthine, 1,3-dimethyl-8-(3,5-dimethoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,5-dimethoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,5-

difluorostyryl)xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-(hydroxy)styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-(acetoxy)styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-(benzyloxy)styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[(4-aminobutyl)oxy]-styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[[4-[[(tertbutyloxy)-carbonyl]amino]butyl]oxy]styryl]xanthine, 1,3,7,-trimethyl-8-[3,5-dimethoxy-4-[(4-amino-trans-butenyl)oxy]styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[(4-acetylamino-trans-butenyl)oxy]styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[(4-t-butyloxycarbonylamino-trans-butenyl)oxy]styryl]xanthine, 1,3,7-trimethyl-8-(2,3,4-trimethoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,4,5-trimethoxystyryl)xanthine, 7-Methyl-1,3-diethyl-8-(3,4,5-trimethoxystyryl)xanthine, 7-Methyl-1,3-diallyll-8-(3,4,5-trimethoxystyryl)xanthine, 1,3-dipropyl-7-methyl-8-(3-chlorostyryl)xanthine, 1,3-dipropyl-7-methyl-8-(3,4-dimethoxystyryl)xanthine, 1,3-dipropyl-7-methyl-8-(3,5-dimethoxystyryl)xanthine, DMPX, ZM241385, or SCH58261.

6. A method as claimed in claim 1, wherein said **antagonist** is 8-(3-chlorostyryl) caffeine.

7. A method as claimed in claim 1 wherein said **antagonist** is administered to said patient prior to a surgical procedure which may cause cardiac ischemic damage.

8. A method as claimed in claim 1, wherein said **antagonist** is administered to said patient during a surgical procedure which may cause cardiac ischemic damage.

9. A method as claimed in claim 1, wherein said **antagonist** is administered to said patient following a surgical procedure which may result in cardiac ischemic damage.

10. A method as claimed in claim 1, wherein said patient is in need of said treatment due to chronic stable angina.

11. A method as claimed in claim 1, wherein said patient is in need of said treatment due to unstable angina.

12. A method as claimed in claim 1, wherein said patient is in need of said treatment due to post-myocardial infarction angina.

13. A method for treating a patient to enhance myocardial responsiveness of heart muscle cells to preconditioning stimuli, comprising administering to a patient in need of said treatment, an A2a receptor **antagonist** in an amount effective to enhance myocardial response to said preconditioning stimuli, without activation of an A3 **adenosine receptor**.

14. A method as claimed in claim 13, wherein said patient is in need of said treatment due to chronic unstable angina.

15. A method as claimed in claim 13, wherein said patient is in need of said treatment due to stable angina.

16. A method as claimed in claim 13, wherein said patient is in need of said treatment due to post-myocardial infarction angina.

17. A method as claimed in claim 13 wherein said **antagonist** is administered to said patient prior to a surgical procedure which may cause cardiac ischemic damage.

18. A method as claimed in claim 13, wherein said **antagonist** is administered to said patient during a surgical procedure which may cause cardiac ischemic damage.

19. A method as claimed in claim 13, wherein said **antagonist** is administered to said patient following a surgical procedure which may result in cardiac ischemic damage.

20. A method as claimed in claim 13, wherein said A2a **antagonist** is a compound selected from the group consisting of 1,3,7-trimethyl-8-styrylxanthine, 1,3,7-trimethyl-8-(2-methoxystyryl)xanthine, 1,3,7-trimethyl-8-(3-methoxystyryl)xanthine, 1,3,7-trimethyl-8-[3-

(trifluoromethyl)styryl]xanthine, 1,3,7-trimethyl-8-(3-nitrostyryl)xanthine, 1,3,7-trimethyl-8-(3-aminostyryl)xanthine, 1,3,7-trimethyl-8-[3-(acetylamino)styryl]xanthine, 1,3,7-trimethyl-8-[3-[3(-carboxyl-1-oxopropyl)amino]-styryl]xanthine, 1,3,7-trimethyl-8-[3-[(tert-butyloxy)carbonyl]amino]-styryl]xanthine, 1,3,7-trimethyl-8-[3-[bis[(tert-butyloxy)carbonyl]amino]-styryl]xanthine, 1,3,7-trimethyl-8-(3-fluorostyryl)xanthine, 1,3,7-trimethyl-8-(4-methoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,4-dimethoxystyryl)xanthine, 1,3-dimethyl-8-(3,5-dimethoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,5-dimethoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,5-difluorostyryl)xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-(hydroxy)styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-(acetoxy)styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-(benzyloxy)styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[(4-aminobutyl)oxy]-styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[[4-[[(tertbutyloxy)-carbonyl]amino]butyl]oxy]styryl]xanthine, 1,3,7,-trimethyl-8-[3,5-dimethoxy-4-[(4-amino-trans-butenyl)oxy]styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[(4-acetylamino-trans-butenyl)oxy]styryl]xanthine, 1,3,7-trimethyl-8-[3,5-dimethoxy-4-[(4-t-butyloxycarbonylamino-trans-butenyl)oxy]styryl]xanthine, 1,3,7-trimethyl-8-(2,3,4-trimethoxystyryl)xanthine, 1,3,7-trimethyl-8-(3,4,5-trimethoxystyryl)xanthine, 7-Methyl-1,3-diethyl-8-(3,4,5-trimethoxystyryl)xanthine, 7-Methyl-1,3-diallyll-8-(3,4,5-trimethoxystyryl)xanthine, 1,3-dipropyl-7-methyl-8-(3-chlorostyryl)xanthine, 1,3-dipropyl-7-methyl-8-(3,4-dimethoxystyryl)xanthine, 1,3-dipropyl-7-methyl-8-(3,5-dimethoxystyryl)xanthine, DMPX, ZM241385, or SCH58261.

L14 ANSWER 39 OF 56 USPATFULL on STN
1998:162350 Stable expression of human A_{2B} **adenosine receptors**, and assays employing the same.
Linden, Joel, Charlottesville, VA, United States
Taylor, Heidi, Charlottesville, VA, United States
Robeva, Anna, Charlottesville, VA, United States
Woodard, Robin, Palmyra, VA, United States
Jin, Xiaowei, Charlottsville, VA, United States
The University of Patent Foundation, Charlottesville, VA, United States (U.S. corporation)
US 5854081 19981229
APPLICATION: US 1996-670175 19960620 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of detecting binding of [^{3} H]1,3-diethyl-8-phenyl-xanthine to a human A_{2B} **adenosine receptor**, comprising contacting said receptor, which is present in an amount of at least about 5 pmol/mg of protein, with said [^{3} H]1,3-diethyl-8-phenyl-xanthine under conditions which permit binding of said [^{3} H]1,3-diethyl-8-phenyl-xanthine to said A_{2B} **adenosine receptor** to occur, washing said **adenosine receptor** to remove any unbound material, and inspecting the resulting sample to determine the presence of said [^{3} H]1,3-diethyl-8-phenyl-xanthine, wherein the presence and amount of said [^{3} H]1,3-diethyl8-phenyl-xanthine correlates with the presence and amount of binding of said [3H]1,3 -diethyl-8-phenyl-xanthine to said A_{2B} **adenosine receptor**.

2. The method of claim 1, wherein said A_{2B} **adenosine receptor** comprises the amino acid sequence for corresponding native A_{2B} **adenosine receptor**, and further comprises recombinantly added marker groups of hexahistidine and the FLAG amino acid sequence Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (SEQ ID NO:1).

3. The method of claim 1, wherein the presence and amount of binding of said [^{3} H]1,3-diethyl-8-phenyl-xanthine is compared with an amount of binding of a target compound with said A_{2B} **adenosine receptor**, and wherein said comparison is indicative of the effectiveness of said target compound as an A_{2B} **adenosine receptor antagonist** or agonist.

4. The method of claim 3, wherein the method of detecting binding is a competitive binding assay.

5. The method of claim 3, wherein said target compound is a potentially

therapeutically active compound.

6. A method of detecting binding of [^{3} H]1,3-diethyl-8-phenyl-xanthine to a human A_{2B} **adenosine receptor**, comprising contacting a membrane with said [^{3} H]1,3-diethyl-8-phenyl-xanthine, wherein said membrane is comprised of a plurality of said A_{2B} **adenosine receptors** which are present in an amount of at least about 5 pmol/mg of protein, under conditions which permit binding of said [^{3} H]1,3-diethyl-8-phenyl-xanthine to said A_{2B} **adenosine receptors** to occur, and detecting binding of said [^{3} H]1,3-diethyl-8-phenyl-xanthine to said A_{2B} **adenosine receptors**.

7. The method of claim 6, wherein said A_{2B} **adenosine receptors** comprise the amino acid sequence for corresponding native A_{2B} **adenosine receptor**, and further comprise recombinantly added marker groups of hexahistidine and the FLAG amino acid sequence Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (SEQ ID NO:1).

=> d l14,cbib,clm,1-19

L14 ANSWER 1 OF 56 USPATFULL on STN
2004:146796 Catheter and implants for the delivery of therapeutic agents to tissues.
Palasis, Maria, Wellesley, MA, United States
Barry, James J., Marlborough, MA, United States
SciMed Life Systems, Inc., Maple Grove, MN, United States (U.S. corporation)
US 6749617 B1 20040615
APPLICATION: US 2000-709031 20001108 (9)
PRIORITY: US 1997-64210P 19971104 (60)
DOCUMENT TYPE: Utility; GRANTED.

CLM What is claimed is:

1. A therapeutic implant system, comprising: an elongate catheter having a distal end including a lumen, and a therapeutic carrier disposed within the lumen, the carrier adapted to allow therapeutic to be released to a target site from the carrier after the carrier has been deployed from the catheter at the target site, the carrier having a solid form at least after it is deployed from the catheter.

2. The system in accordance with claim 1, wherein the carrier is bio-stable.

3. The system in accordance with claim 1, wherein the carrier is biodegradable.

4. The system in accordance with claim 1, wherein the therapeutic agent is selected from the agents consisting of VEGF, FGF, PDGF, estrogen and combinations thereof.

5. The system in accordance with claim 1, wherein the therapeutic agent includes genes effecting the production of growth factors.

6. The system in accordance with claim 1, wherein the therapeutic agent includes genetically engineered cells.

7. The system in accordance with claim 1, wherein the therapeutic agent includes healthy tissue.

8. The system in accordance with claim 1, wherein the therapeutic agents are selected from the agents consisting of positive inotripic, diuretics vasodilators, nuerohormonal **antagonists**, calcium, channel blockers, anti-ischemic agents, anti-arrhythmics, anticoagulants, natiruretic peptides, growth hormones, and **adenosine receptor antagonists** and mixtures thereof.

9. The system in accordance with claim 1, wherein the therapeutic agents are selected from the agents consisting of AKT kinases, adenylyl cylase VI, angiogenisis inducing agents and mixtures thereof.

10. The system in accordance with claim 1, wherein the therapeutic agents are selected from the agents comprising cytoxic proteins, cytostatic agents, genes, anti-angiogenic molecules and mixtures thereof.

11. The system in accordance with claim 1, wherein the catheter includes a first lumen and a second lumen.

12. The system in accordance with claim 11, wherein an exit orifice of the second lumen is positioned within the first lumen.

13. The system in accordance with claim 12 wherein the first lumen and the second lumen share a longitudinal axis.

14. The system in accordance with claim 13 wherein the first lumen is concentric with the second lumen.

15. The system in accordance with claim 11 wherein the carrier is in the first lumen and a therapeutic is in the second lumen.

16. The system in accordance with claim 1 Wherein the lumen contains a radiopaque material.

17. The system in accordance with claim 11 wherein the first lumen contains a polymer cross-linking agent and the second lumen contains a polymer.

L14 ANSWER 2 OF 56 USPATFULL on STN
2004:14935 Methods of inhibiting tumor growth using **adenosine receptor** activated cells.
Neely, Constance, Raleigh, NC, United States
Endacea, Inc., Research Triangle Park, NC, United States (U.S. corporation)
US 6680052 B1 20040120
APPLICATION: US 1999-465478 19991216 (9)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of inhibiting cancer in a subject, comprising: (a) obtaining a sample of treatment cells from a subject, wherein said treatment cells are selected from the group consisting of macrophages, cultured monocytes and cultured splenocytes; (b) priming said treatment cells by contact with a priming agent in an amount sufficient to prime said treatment cells; (c) activating said treatment cells by contact with an A_1 **adenosine receptor** agonist in an amount sufficient and for a time sufficient to induce cytotoxicity in said treatment cells, wherein said A_1 **adenosine receptor** agonist comprises adenosine; and then (d) administering said cytotoxic treatment cells to the subject in an effective cancer-inhibiting amount.

2. The method of claim 1 wherein said treatment cells are monocytes, and said monocytes are cultured to provide macrophages for priming in step (b).

3. The method of claim 1 wherein said priming agent is selected from the group consisting of phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon gamma (IFNγ), granulocyte-macrophage colony stimulating factor (GMCSF), and f-met-leu-phe (FMLP).

4. The method of claim 1 wherein said subject is human.

5. The method of claim 1 further comprising the step of contacting said treatment cells to an A_2 **adenosine receptor antagonist.**

6. The method of claim 1 further comprising, prior to step (b), subjecting said treatment cells to a period of hypoxia and re-oxygenation sufficient to increase A_1 **adenosine receptor** activity.

7. The method of claim 1 further comprising contacting said treatment cells to an allosteric enhancer in an amount effective to increase the binding of A_1 **adenosine receptor** agonists to A_1 **adenosine receptors.**

8. The method of claim 1 further comprising contacting said treatment cells to dexamethasone in an amount effective to increase the number of A_1 **adenosine receptor** receptors on said treatment cells.

9. The method of claim 1 further comprising contacting said treatment

cells to a protein kinase inhibitor.

10. The method of claim 1 wherein said administering step is carried out by administering said cytotoxic treatment cells systemically to said subject.

11. The method of claim 1 wherein said administering step is carried out by administering said cytotoxic treatment cells directly to tissue containing said cancer.

L14 ANSWER 3 OF 56 USPATFULL on STN
2004:7842 2-Aminopyridine compounds and use thereof as drugs.
Harada, Hitoshi, Ibaraki, JAPAN
Asano, Osamu, Ibaraki, JAPAN
Miyazawa, Shuhei, Ibaraki, JAPAN
Ueda, Masato, Ibaraki, JAPAN
Yasuda, Masahiro, Ibaraki, JAPAN
Yasuda, Nobuyuki, Ibaraki, JAPAN
US 2004006082 A1 20040108
APPLICATION: US 2003-333689 A1 20030123 (10)
WO 2001-JP6870 20010809
PRIORITY: JP 2000-245056 20000811
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A compound represented by the formula: ##STR228## (wherein R^1 represents cyano group, carboxyl group or an optionally substituted carbamoyl group; R^2represents hydrogen atom, hydroxyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aromatic hydrocarbon cyclic group or an optionally substituted 5- to 14-membered aromatic heterocyclic group; and R^3 and R^4 are the same as or different from each other and each represents a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkenyl group, a C_{6-14} aromatic hydrocarbon cyclic group, a 5- to 14-membered non-aromatic heterocyclic group or a 5- to 14-membered aromatic heterocyclic group which may have a substituent group, respectively, provided that the cases where (1) R^1 is cyano group, R^2 is 4-bromo-2-thienyl group, R^3 is 3,4-dimethoxyphenyl group and R^4 is 2-thienyl group, (2) R^1 is cyano group, R^2 is hydrogen atom, and each of R^3 and R^4 is phenyl group, (3) R^1 is cyano group, R^2 is 4-chlorophenyl group, R^3 is phenyl group and R^4 is 4-(3,4-dichlorophenyl)-1-oxo-2(1H)-phthalazinyl group, (4) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 1-piperazinyl group, (5) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is a 1-pyridyl group, (6) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 4-diphenylmethyl-1-piperazinyl group, (7) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 4-morpholinyl group, (8) R^1 is cyano group, R^2 is 4-methylphenyl group, and each of R^3 and R^4 is phenyl group and (9) R^1 is cyano group, and each of R^2, R^3 and R^4 is phenyl group are excluded) or a salt thereof.

2. The compound according to claim 1 or a salt thereof, in which R^1 is cyano group.

3. The compound according to claim 1 or a salt thereof, in which R^1 is a carbamoyl group represented by the formula: ##STR229## wherein R^5 and R^6 are the same as or different from each other and each represents hydrogen atom, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{6-14} aromatic hydrocarbon cyclic group or an optionally substituted 5- to 14-membered aromatic heterocyclic group.

4. The compound according to claim 1 or a salt thereof, in which R^2 is a C_{6-14} aromatic hydrocarbon cyclic group or 5- to 14-membered aromatic heterocyclic group, each of which may have a substituent group.

5. The compound according to claim 1 or a salt thereof, in which R^2 is a phenyl group, naphthyl group, pyridyl group, thienyl group or furyl group, each of which may have a substituent group.

6. The compound according to claim 1 or a salt thereof, in which R^2 is a phenyl group which may be substituted with a halogen atom.

7. The compound according to claim 1 or a salt thereof, in which R^2 is hydrogen atom.

8. The compound according to claim 1 or a salt thereof, in which R^3 and R^4 are the same as or different from each other and each represents a C_{6-14} aromatic hydrocarbon cyclic group or a 5- to 14-membered aromatic heterocyclic group, each of which may have a substituent group.

9. The compound according to claim 1 or a salt thereof, in which R^3 and R^4 are the same as or different from each other and each represents a phenyl group, pyrrolyl group, pyridinyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, thienyl group, thiazolyl group, furyl group, naphthyl group, quinolinyl group, isoquinolinyl group, phthalazinyl group, naphthyridinyl group, indolyl group or isoindolyl group, each of which may have a substituent group.

10. The compound according to claim 1 or a salt thereof, in which each of R^3 and R^4 represents a phenyl group, pyridyl group, thienyl group or furyl group which may have a substituent group, respectively.

11. The compound according to claim 1 or a salt thereof, in which R^3 and/or R^4 represent a 5- to 14-membered non-aromatic heterocyclic group, a C_{6-14} aromatic hydrocarbon cyclic group or a 5- to 14-membered aromatic heterocyclic group, each of which may be substituted with at least one group selected from the following substituent group a. <substituent group a> a group consisting of (1) hydroxyl group, (2) a halogen atom, (3) cyano group, (4) nitro group, (5) a C_{1-6} alkyl group, C_{2-6} alkenyl group or C_{2-6} alkynyl group, each of which may be substituted with at least one group selected from (i) hydroxyl group, (ii) cyano group, (iii) halogen atom, (iv) C_{1-6} alkylamino group, (v) di(C_{1-6} alkyl)amino group, (vi) C_{2-6} alkenylamino group, (vii) di(C_{2-6} alkenyl)amino group, (viii) C_{2-6} alkynylamino group, (ix) di(C_{2-6} alkynyl)amino group, (x) N-C_{1-6} alkyl-N-C_{2-6} alkenylamino group, (xi) N-C_{1-6} alkyl-N-C_{2-6} alkynylamino group, (xii) N-C_{2-6} alkenyl-N-C_{2-6} alkynylamino group, (xiii) aralkyloxy group, (xiv) TBDMS oxy group, (xv) C_{1-6} alkylsulfonylamino group, (xvi) C_{1-6} alkylcarbonyloxy group, (xvii) C_{2-6} alkenylcarbonyloxy group, (xviii) C_{2-6} alkynylcarbonyloxy group, (xix) N-C_{1-6} alkylcarbamoyl group, (xx) N-C_{2-6} alkenylcarbamoyl group and (xxi) N-C_{1-6} alkynylcarbamoyl group, (6) a C_{1-6} alkoxy group, C_{2-6} alkenyloxy group or C_{2-6} alkynyloxy group, each of which may be substituted with at least one group selected from (i) C_{1-6} alkylamino group, (ii) aralkyloxy group and (iii) hydroxyl group, (7) a C_{1-6} alkylthio group, C_{2-6} alkenylthio group or C_{2-6} alkynylthio group, each of which may be substituted with at least one group selected from (i) hydroxyl group, (ii) nitrile group, (iii) halogen atom, (iv) C_{1-6} alkylamino group, (v) aralkyloxy group, (vi) TBDMS oxy group, (vii) C_{1-6} alkylsulfonylamino group, (viii) C_{1-6} alkylcarbonyloxy group and (ix) C_{1-6} alkylcarbamoyl group, (8) a carbonyl group substituted with a group selected from (i) C_{1-6} alkoxy group, (ii) amino group, (iii) C_{1-6} alkylamino group, (iv) di(C_{1-6} alkyl)amino group, (v) C_{2-6} alkenylamino group, (vi) di (C_{2-6} alkenyl)amino group, (vii) C_{2-6} alkynylamino group, (vii) di(C_{2-6} alkynyl)amino group, (viii) N-C_{1-6} alkyl-N-C_{2-6} alkenylamino group, (ix) N-C_{1-6} alkyl-N-C_{2-6} alkynylamino group and (x) N-C_{2-6} alkenyl-N-C_{2-6} alkynylamino group, (9) an amino group which may be substituted with one or two groups selected from (i) C_{1-6} alkyl group, (ii) C_{2-6} alkenyl group, (iii) C_{2-6} alkynyl group, (iv) C_{1-6} alkylsulfonyl group, (v) C_{2-6} alkenylsulfonyl group, (vi) C_{2-6} alkynylsulfonyl group, (vii) C_{1-6} alkylcarbonyl group, (viii) C_{2-6} alkenylcarbonyl group and (ix) C_{2-6} alkynylcarbonyl group, (10) a C_{1-6} alkylsulfonyl group, (11) a C_{2-6} alkenylsulfonyl group, (12) a C_{2-6} alkynylsulfonyl group, (13) a C_{1-6} alkylsulfinyl group, (14) a C_{2-6} alkenylsulfinyl group, (15) a C_{2-6} alkynylsulfinyl group, (16) formyl group, (17) a C_{3-8} cycloalkyl group or C_{3-8}

cycloalkenyl group, each of which may be substituted with at least one group selected from (i) hydroxyl group, (ii) halogen atom, (iii) nitrile group, (iv) C_{1-6} alkyl group, (v) C_{1-6} alkoxy group, (vi) C_{1-6} alkoxy-C_{1-6} alkyl group and (vii) aralkyl group, (18) a 5- to 14-membered non-aromatic heterocyclic group which may be substituted with at least one group selected from (i) hydroxyl group, (ii) halogen atom, (iii) nitrile group, (iv) C_{1-6} alkyl group, (v) C_{1-6} alkoxy group, (vi) C_{1-6} alkoxy-C_{1-6} alkyl group and (vii) aralkyl group, (19) a C_{6-14} aromatic hydrocarbon cyclic group which may be substituted with at least one group selected from (i) hydroxyl group, (ii) halogen atom, (iii) nitrile group, (iv) C_{1-6} alkyl group, (v) C_{1-6} alkoxy group, (vi) C_{1-6} alkoxy-C_{1-6} alkyl group and (vii) aralkyl group, and (20) a 5- to 14-membered aromatic heterocyclic group which may be substituted with at least one group selected from (i) hydroxyl group, (ii) halogen atom, (iii) nitrile group, (iv) C_{1-6} alkyl group, (v) C_{1-6} alkoxy group, (vi) C_{1-6} alkoxy-C_{1-6} alkyl group and (vii) aralkyl group.

12. The compound according to claim 1 or a salt thereof, in which R^3 and/or R^4 represent a phenyl group, pyridyl group, thienyl group or furyl group, each of which may be substituted with at least one group selected from hydroxyl group, a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group.

13. The compound according to claim 1 or a salt thereof, in which R^3 or R^4 is a 6-oxo-1,6-dihydropyridyl group which may have a substituent group.

14. The compound according to claim 1 represented by the formula: ##STR230## (wherein R^1 represents cyano group, carboxyl group or an optionally substituted carbamoyl group; R^2 represents hydrogen atom, hydroxyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{6-14} aromatic hydrocarbon cyclic group or an optionally substituted 5- to 14-membered aromatic heterocyclic group; R^7 represents a group selected from the following substituent group b; R^8 represents a C_{6-14} aromatic hydrocarbon cyclic group or a 5- to 14-membered aromatic heterocyclic group which may have a substituent group, respectively; and ring A represents a nitrogen-containing 6-membered ring which may be substituted with 1 to 4 groups selected from the following substituent group b. <substituent group b> a group consisting of hydrogen atom, a halogen atom, hydroxyl group, nitro group, cyano group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group, an optionally substituted C_{2-6} alkynyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{2-6} alkenyloxy group, an optionally substituted C_{2-6} alkynyloxy group, an optionally substituted C_{1-6} alkylthio group, an optionally substituted C_{2-6} alkenylthio group, an optionally substituted C_{2-6} alkynylthio group, a C_{2-7} fatty acyl group, an optionally substituted carbamoyl group, an arylacyl group, a heteroaryl acyl group, an optionally substituted amino group, an optionally substituted C_{1-6} alkylsulfonyl group, an optionally substituted C_{2-6} alkenylsulfonyl group, an optionally substituted C_{2-6} alkynylsulfonyl group, an optionally substituted C_{1-6} alkylsulfinyl group, an optionally substituted C_{2-6} alkenylsulfinyl group, an optionally substituted C_{2-6} alkynylsulfinyl group, formyl group, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted C_{3-8} cycloalkenyl group, an optionally substituted 5- to 14-membered non-aromatic heterocyclic group, an optionally substituted C_{6-14} aromatic hydrocarbon cyclic group and an optionally substituted 5- to 14-membered aromatic heterocyclic group) or a salt thereof.

15. The compound according to claim 14 or a salt thereof, in which R^1 is cyano group.

16. The compound according to claim 14 or a salt thereof, in which R^1 is carboxyl group.

17. The compound according to claim 14 or a salt thereof, in which R^1 is a carbamoyl group represented by the formula: ##STR231## in

which R^5 and R^6 have the same meanings as defined above.

18. The compound according to claim 14 or a salt thereof, in which R^2 is hydrogen atom.

19. The compound according to claim 14 or a salt thereof, in which R^7 and the substituent groups other than R^7 in the ring A are selected from the above-mentioned substituent group a.

20. The compound according to claim 14 or a salt thereof, in which R^7 is hydrogen atom, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{2-6} alkenyl group or an optionally substituted C_{1-6} alkoxy group.

21. The compound according to claim 14 or a salt thereof, in which R^8 is a phenyl group, pyridyl group, furyl group or a thienyl group, each of which may have a substituent group.

22. The compound according to claim 14 or a salt thereof, in which R^8 is a phenyl group, pyridyl group, furyl group or a thienyl group, each of which may be substituted with a halogen atom.

23. The compound according to claim 1, in which the compound is any one selected from 2-amino-6-(2-furyl)-5-(4-pyridyl)-3-pyridinecarbonitrile, 2-amino-6-(3-fluorophenyl)-5-(4-pyridyl)-3-pyridinecarbonitrile, 2-amino-6-(2-furyl)-5-(4-methoxy-3-pyridyl)-3-pyridinecarbonitrile, 2-amino-6-(2-furyl)-5-(6-oxo-1,6-dihydro-3-pyridinyl)nicotinonitrile, 2-amino-5-(1-ethyl-6-oxo-1,6-dihydro-3-pyridinyl)-6-(2-furyl)nicotinonitrile, 2-amino-6-(2-furyl)-5-(1-methyl-6-oxo-1,6-dihydro-3-pyridinyl)nicotinonitrile, 2-amino-6-(3-fluorophenyl)-5-(6-oxo-1,6-dihydro-3-pyridinyl)nicotinonitrile and 2-amino-6-(3-fluorophenyl)-5-(1-methyl-6-oxo-1,6-dihydro-3-pyridinyl)nicotinonitrile, or a salt thereof.

24. A pharmaceutical composition comprising a compound represented by the formula: ##STR232## (wherein R^1 represents cyano group, carboxyl group or an optionally substituted carbamoyl group; R^2 represents hydrogen atom, hydroxyl group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aromatic hydrocarbon cyclic group or an optionally substituted 5- to 14-membered aromatic heterocyclic group; and R^3 and R^4 are the same as or different from each other and each represents a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkenyl group, a C_{6-14} aromatic hydrocarbon cyclic group, a 5- to 14-membered non-aromatic heterocyclic group or a 5- to 14-membered aromatic heterocyclic group which may have a substituent group, respectively, provided that the cases where (1) R^1 is cyano group, R^2 is 4-bromo-2-thienyl group, R^3 is 3,4-dimethoxyphenyl group and R^4 is 2-thienyl group, (2) R^1 is cyano group, R^2 is hydrogen atom and each of R^3 and R^4 is phenyl group, (3) R^1 is cyano group, R^2 is 4-chloro-phenyl group, R^3 is phenyl group and R^4 is 4-(3,4-dichlorophenyl)-1-oxo-2(1H)-phthalazinyl group, (4) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 1-piperazinyl group, (5) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 1-pyridyl group, (6) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 4-diphenylmethyl-1-piperazinyl group, (7) R^1 is cyano group, R^2 is hydrogen atom, R^3 is 4-pyridyl group and R^4 is 4-morpholinyl group, (8) R^1 is cyano group, R^2 is 4-methylphenyl group and each of R^3 and R^4 is phenyl group, and (9) R^1 is cyano group and each of R^2, R^3 and R^4 is phenyl group are excluded) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

25. The composition according to claim 24, which is an agent for treating or preventing a disease to which an **adenosine receptor** relates.

26. The composition according to claim 24, which is an agent for treating or preventing a disease to which an adenosine A_2 receptor relates.

27. The composition according to claim 24, which is an agent for treating or preventing a disease to which an adenosine A_{2B} receptor relates.

28. The composition according to claim 24, which is an **adenosine**

receptor antagonist.

29. The composition according to claim 24, which is an adenosine A_2 receptor **antagonist**.

30. The composition according to claim 24, which is an adenosine A_{2B} receptor **antagonist**.

31. The composition according to claim 24, which is used for promoting defecation.

32. The composition according to claim 24, which is an agent for treating, preventing or improving constipation.

33. The composition according to claim 24, in which the constipation is functional constipation.

34. The composition according to claim 24, which is an agent for treating irritable bowel syndrome, constipation accompanying irritable bowel syndrome, organic constipation, constipation accompanying enteroparalytic ileus, constipation accompanying congenital digestive tract dysfunction or constipation accompanying ileus.

35. The composition according to claim 24, which is used for evacuating intestinal tracts at the time of examination of digestive tracts or before and after an operation.

36. The composition according to claim 24, which is an agent for treating or preventing diabetes, diabetic complications, diabetic retinopathy, obesity or asthma.

37. The composition according to claim 24, which is a hypoglycemic agent, an improving agent for impaired glucose tolerance or a potentiating agent for insulin sensitivity.

38. The composition according to claim 24, which is a hypotensive agent, a diuretic, a therapeutic agent for osteoporosis, an anti-Parkinson's disease agent, an anti-Alzheimer's disease agent, a therapeutic agent for inflammatory intestinal diseases or a therapeutic agent for Crohn's disease.

39. Use of the compound according to claim 1 or a pharmacologically acceptable salt thereof for producing an agent for treating or preventing a disease to which an **adenosine receptor** relates.

40. A method of treating or preventing a disease to which an **adenosine receptor** relates, by administering a pharmacologically effective dose of the compound according to claim 1 or a pharmacologically acceptable salt thereof to a patient.

L14 ANSWER 4 OF 56 USPATFULL on STN
2003:195054 Modulation of histone deacetylase.
Adcock, Ian, London, UNITED KINGDOM
Lim, Samson, New South Wales, AUSTRALIA
Ito, Kazuhiro, Tokyo, JAPAN
Barnes, Peter John, London, UNITED KINGDOM
US 2003134865 A1 20030717
APPLICATION: US 2003-220342 A1 20030113 (10)
WO 2001-GB905 20010302
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A screening method for identifying a drug-like compound or lead compound for the development of a drug-like compound in which (1) a xanthine or related compound is exposed to a histone deacetylase, (2) the binding of the compound to the histone deacetylase is measured or the change in the activity of the histone deacetylase is measured or the change in the binding of the histone deacetylase to activated glucocorticoid receptor (GR) is measured and (3) any compound capable of the required binding to the histone deacetylase or producing the required change in the activity of the histone deacetylase or its binding to activate glucocorticoid receptor is identified.

2. A screening method for identifying a drug-like compound or lead

compound for the development of a drug-like compound wherein the ability of a xanthine or related compound to modulate the expression of a histone deacetylase gene, or expression from a transcriptional regulatyr sequence derived from a histone deacetylase gene, is measured and any compound capable of effecting the required modulation in the expression of the said histone deacetylase gene, or in the expression from the said transcriptional regulatory sequence, is identified.

3. A method for modulating a histone deacetylase activity wherein the histone deacetylase is exposed to a compound identified or identifiable by the method of claim 1.

4. Use of a compound identified or identifiable by the method of claim 1 in a method for modulating a histone deacetylase activity wherein the histone deacetylase is exposed to a compound identified or identifiable by the method of claim 1.

5. The use or method of any of the preceding claims wherein the xanthine is a methylxanthine.

6. The use or method of claim 5 wherein the methylxanthine is theophylline or a salt thereof.

7. The use or method of any one of claims 1 to 6 performed in vitro.

8. The use or method of any one of claims 1 to 7 wherein the histone deactetylase is or comprises histone deacetylase 1, histone deacetylase 2 and/or histone deacetylase 3.

9. The method of any of claims 1, 2 or 5 to 8 fiber comprising the steps of (1) exposing the compound to a phosphodiesterase activity and determining the effect of the compound on the phosphodiesterase activity and/or (2) exposing the compound to an **adenosine receptor** and determining the activity of the compound as an **adenosine receptor antagonist** and (3) any compound capable of the required effect on phosphodiesterase activity and/or having the required activity as an **adenosine receptor antagonist** is identified.

10. The method of any of claims 1, 2 or 5 to 9 wherein the required change in the activity of the histone deacetylase is an increase in the said activity or wherein the required change in the binding of the histone deacetylase to activated glucocorticoid receptor (GR) is an increase in the said binding.

11. The method of any of claims 1, 2 or 5 to 10 wherein the xanthine or related compound is exposed to a histone deacetylase or the ability of a xanthine or related compound to modulate the expression of a histone deacetylase is measured in the presence of a glucocorticoid.

12. A compound identifiable by the screening method of any one of claims 1, 2 or 5 to 11 wherein the compound is not theophylline, caffeine, acepifylline, bamifylline, bufylline, cafaminol, cafedrine, diprophylline, doxofylline, enprofylline, etamiphylline, etofylline, proxyphylline, suxamidofylline, theobromine or a salt thereof, or a glucocorticoid or pyridinylimidazole compound.

13. The compound of claim 12 for use in medicine.

14. Use of a compound identifiable by the screening method of any one of claims 1, 2 or 5 to 11 in the manufacture of a medicament for the treatment of a patient in need of modulation of histone deacetylase activity, wherein the patient is not in need of modulation of histone deacetylase activity on account of having asthma or other inflammatory airway disease.

15. Use of a compound identifiable by the screening method of claim 10 in the manufacture of a medicament for the treatment of a patient in need of an increase in histone deacetylase activity or a decrease in histone acetylation, wherein the patient is not in need of modulation of histone deacetylase activity on account of having asthma or other inflammatory airway disease.

16. Use of a compound according to claim 12 in the manufacture of a medicament for the treatment of a patient with asthma or other airway disease or other chronic inflammatory disease.

17. Use of a compound identifiable by the screening method of any of claims 1, 2 or 5 to 11 in the manufacture of a medicament for the treatment of a disorder of cellular differentiation and/or proliferation in which excessive phosphodiesterase 3 or 4 activity or excessive **adenosine receptor** activity have not been implicated, but in which histone deacetylase or the level of histone acetylation has been implicated in causing or exacerbating the disorder.

18. A method of treatment of a patient in need of modulation of histone deacetylase activity, comprising administering an effective amount of a compound identified or identifiable by the screening method of any one of claims 1, 2 or 5 to 11, wherein the patient is not in need of modulation of histone deacetylase activity on account of having asthma or other inflammatory airway disease.

19. A method of treatment of a patient in need of an increase in histone deacetylase activity or a decrease in histone acetylation, comprising administering an effective amount of a compound identified or identifiable by the screening method of claim 10, wherein the patient is not in need of modulation of histone deacetylase activity on account of having asthma or other inflammatory airway disease.

20. A method of treatment of a patient with asthma or other inflammatory airway disease, comprising administering an effective amount of a compound according to claim 12.

21. A method of treatment of a patient in need of modulation of histone deacetylase or histone acetylation, or with a disorder of cellular differentiation and/or proliferation in which excessive phosphodiesterase 3 or 4 activity or excessive **adenosine receptor** activity have not been implicated, but in which histone deacetylase or the level of histone acetylation has been implicated in causing or exacerbating the condition, comprising administering an effective amount of a compound identifiable by the screening method of any of claims 1, 2 or 5 to 11.

22. The use or method of any of claims 14 to 21 wherein a glucocorticoid is, has been, or will be administered to the patient.

23. A kit of parts comprising a glucocorticoid and a compound according to claim 12.

24. A kit of parts suitable for carrying out a method according to any one of claims 1, 2 or 5 to 11 comprising a histone deacetylase, a xanthine or related compound.

25. A kit of parts according to claim 24 further comprising a glucocorticoid.

26. Use of a histone deacetylase in a method of identifying an anti-asthmatic agent.

27. A screening method for identifying a drug-like compound or lead compound for the development of a drug-like compound for treating asthma or other inflammatory airway disease in which (1) a test compound is exposed to a histone deacetylase, (2) the binding of the compound to the histone deacetylase is measured or the change in the activity of the histone deacetylase is measured or the change in the binding of the histone deacetylase to activated glucocorticoid receptor (GR) is measured and (3) any compound capable of the required binding to the histone deacetylase or producing the required change in the activity of the histone deacetylase or its binding to activated glucocorticoid receptor is identified.

28. A screening method for identifying a drug-like compound or lead compound for the development of a drug-like compound for treating asthma or other inflammatory airway disease, ulcerative colitis and/or rheumatoid arthritis, wherein the ability of a test compound to modulate the expression of a histone deacetylase gene, or expression from a transcriptional regulatory sequence derived from a histone deacetylase gene, is measured and any compound capable of effecting the required modulation in the expression of the said histone deacetylase gene, or in the expression from the said transcriptional regulatory sequence, is identified.

29. Use of a compound which increases histone deacetylase activity in the manufacture of a medicament for treatment of a patient with asthma or other inflammatory airway disease, wherein the compound is not theophylline, caffeine, acepifylline, bamifylline, bufylline, cafaminol, cafedrine, diprophylline, doxofylline, enprofylline, etamiphylline, etofylline, proxyphylline, suxamidofylline, theobromine or a salt thereof, or a glucocorticoid or pyridinylimidazole compound.

30. A method of treatment of a patient with asthma or other inflammatory airway disease comprising administering an effective amount of a compound which increases histone deacetylase activity, wherein the compound is not theophylline, caffeine, acepifylline, bamifylline, bufylline, cafaminol, cafedrine, diprophylline, doxofylline, enprofylline, etamiphylline, etofylline, proxyphylline, suxamidofylline, theobromine or a salt thereof, or a glucocorticoid or pyridinylimidazole compound.

31. A composition comprising a compound according to claim 12 and a pharmaceutically acceptable excipient.

L14 ANSWER 5 OF 56 USPATFULL on STN
2003:134579 Methods and compositions for reducing ischemic injury of the heart by administering **adenosine receptor** agonists and **antagonists**.
Liang, Bruce T., Merion Station, PA, UNITED STATES
Jacobson, Kenneth A., Silver Springs, MD, UNITED STATES
US 2003092668 A1 20030515
APPLICATION: US 2001-800274 A1 20010305 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for preventing or reducing ischemic damage to the heart, in a patient in need thereof, comprising administering to said patient a partial agonist having affinity for the A1 **adenosine receptors** in an amount effective to activate the A1 receptors in the heart of said patient.

2. A method as claimed in claim 1, wherein said partial agonist is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

3. A method as claimed in claim 1, wherein said partial agonist is 8-butylamino-N6-cyclopentyladenosine.

4. A method as claimed in claim 1 wherein said partial agonist is administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

5. A method as claimed in claim 1, wherein said partial agonist is administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

6. A method as claimed in claim 1, wherein said agonist is administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

7. A method as claimed in claim 1, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, post myocardial infarction angina.

8. A method as claimed in claim 1, wherein said patient is in need of such treatment due to acute myocardial infarction.

9. A method for preventing or reducing ischemic damage to the heart, in a patient in need thereof, comprising administering to said patient a partial agonist having affinity for the A3 **adenosine receptors** in an amount effective to activate the A3 receptors in the heart of said patient.

10. A method as claimed in claim 9, wherein said partial agonist is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and

cardiac perfusion.

11. A method as claimed in claim 9, wherein said partial agonist is selected from the group consisting of (1'R,2'R,3'S,4'R,5'S)-4-{2-Chloro-6-[(3-iodophenylmethyl) amino]purin-9-yl}-1-(hydroxymethyl)bicyclo[3.1.0]-hexane-2,3-diol (MRS1760) and (1'R,2'R,3'S,4'R,5'S)-1-(Hydroxymethyl)-4-{6-[(3-iodo-phenylmethyl)amino]purin-9-yl}bicyclo[3.1.0]hexane-2,3-diol(MRS1743).

12. A method as claimed in claim 9 wherein said partial agonist is administered to said patient prior to a surgical procedure having potential to cause cardiac ischemic damage.

13. A method as claimed in claim 9, wherein said partial agonist is administered to said patient during a surgical procedure having potential to cause cardiac ischemic damage.

14. A method as claimed in claim 9, wherein said agonist is administered to said patient following a surgical procedure having potential to result in cardiac ischemic damage.

15. A method as claimed in claim 9, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, post myocardial infarction angina.

16. A method as claimed in claim 9, wherein said patient is in need of such treatment due to acute myocardial infarction.

17. A method for preventing or reducing apoptotic cell death mediated damage to the heart, in a patient in need thereof, comprising administering to said patient an agonist having affinity for both the A1 and A3 **adenosine receptors** in an amount effective to activate A3 and A1 receptors in the heart of said patient thereby reducing apoptosis.

18. A method as claimed in claim 17, wherein said agonist is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

19. A method as claimed in claim 17, wherein said agonist is selected from the group of compounds listed in Table II.

20. A method as claimed in claim 17, wherein said agonist is N^6-((2-trifluoromethyl)carbamoyl) adenosine-5'uronamide.

21. A method as claimed in claim 17, wherein said agonist is N^6-((3-iodophenyl)carbamoyl) adenosine-5'uronamide.

22. A method as claimed in claim 17 wherein said agonist is a binary conjugate which has affinity for, and activates the A1 and A3 **adenosine receptors** simultaneously.

23. A method as claimed in claim 17 wherein said agonist is administered to said patient prior to a surgical procedure having potential to cause cardiac apoptotic cell death.

24. A method as claimed in claim 17, wherein said agonist is administered to said patient during a surgical procedure having potential to cause cardiac apoptotic cell death.

25. A method as claimed in claim 17, wherein said agonist is administered to said patient following a surgical procedure having potential to result in cardiac apoptotic cell death.

26. A method as claimed in claim 17, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, post myocardial infarction angina.

27. A method as claimed in claim 17, wherein said patient is in need of such treatment due to acute myocardial infarction.

28. A method as claimed in claim 17, wherein said apoptotic cell death is caused by a condition selected from the group consisting of idiopathic cardiomyopathy, cardiomyopathy induced by drugs,

cardiomyopathy induced by chronic alcoholism, familial cardiomyopathy, viral myocarditis and cardiomyopathy induced by immunological rejection after heart transplantation.

29. A method for preventing or reducing apoptotic cell death mediated damage to the heart, in a patient in need thereof, comprising administering to said patient a mixed agonist having affinity for the A3 and A1 **adenosine receptors** and an **antagonist** having affinity for the A2a **adenosine receptor** in amounts effective to activate said A3 and A1 receptors and inhibit activation of said A2a receptor in the heart of said patient.

30. A method as claimed in claim 29, wherein said agonist and said **antagonist** are delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

31. A method as claimed in claim 29, wherein said agonist is selected from the group of compounds listed in Table II.

32. A method as claimed in claim 29 wherein said **antagonist** is selected from the group of compounds listed in Table III.

33. A method as claimed in claim 29, wherein said agonist is N^6-((2-trifluoromethyl)carbamoyl) adenosine-5'uronamide.

34. A method as claimed in claim 29, wherein said agonist is N^6-((3-iodophenyl) carbamoyl) adenosine-5'uronamide.

35. A method as claimed in claim 29, wherein said agonist is selected from the group consisting of MRS 584, MRS 479, MRS 537 or MRS 1340.

36. A method as claimed in claim 29, wherein said **antagonist** is selected from the group consisting of CSC, DMPX, ZM241385 or SCH58261.

37. A method as claimed in claim 29, wherein said agonist and said **antagonist** are administered to said patient prior to a surgical procedure having potential to cause cardiac apoptotic cell death.

38. A method as claimed in claim 29, wherein said agonist and said **antagonist** are administered to said patient during a surgical procedure having potential to cause cardiac apoptotic cell death.

39. A method as claimed in claim 29, wherein said agonist and said **antagonist** are administered to said patient following a surgical procedure having potential to result in cardiac apoptotic cell death.

40. A method as claimed in claim 29, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

41. A method as claimed in claim 29, wherein said patient is in need of said treatment due to acute myocardial infarction.

42. A method as claimed in claim 29, wherein said apoptotic cell death is caused by a condition selected from the group consisting of idiopathic cardiomyopathy, cardiomyopathy induced by drugs, cardiomyopathy induced by chronic alcoholism, familial cardiomyopathy, viral myocarditis and cardiomyopathy induced by immunological rejection after heart transplantation.

43. A method for preventing or reducing apoptotic cell death mediated damage to the heart, in a patient in need thereof, comprising administering to said patient a binary conjugate, which acts as an adenosine A3 receptor agonist while simultaneously inhibiting the activation of A2a receptors in an amount effective to enhance myocardial response to said preconditioning stimuli.

44. A method as claimed in claim 43, wherein said patient is in need of such treatment due to a cardiac condition selected from the group consisting of chronic stable angina, unstable angina, post-myocardial infarction angina or acute myocardial infarction.

45. A method as claimed in claim 43 wherein said agonist is administered

to said patient prior to a surgical procedure which may cause cardiac apoptotic cell death.

46. A method as claimed in claim 43, wherein said agonist is administered to said patient during a surgical procedure having potential to cause cardiac apoptotic cell death.

47. A method as claimed in claim 43, wherein said agonist is administered to said patient following a surgical procedure which may result in cardiac apoptotic cell death.

48. A method as claimed in claim 43, wherein said apoptotic cell death is caused by a condition selected from the group consisting of idiopathic cardiomyopathy, cardiomyopathy induced by drugs, cardiomyopathy induced by chronic alcoholism, familial cardiomyopathy, viral myocarditis and cardiomyopathy induced by immunological rejection after heart transplantation.

49. A method for preventing or reducing apoptotic cell death mediated damage to the heart, in a patient in need thereof, comprising administering to said patient both an adenosine A3 receptor agonist and at least one adenosine A1 receptor agonist in an amount effective to activate the A1 and A3 **adenosine receptors** in the heart of said patient.

50. A method as claimed in claim 49, wherein said agonists are delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

51. A method as claimed in claim 49, wherein said agonist and said agonists are administered to said patient prior to a surgical procedure having potential to cause cardiac apoptotic cell death.

52. A method as claimed in claim 49, wherein said agonist and said **antagonist** are administered to said patient during a surgical procedure having potential to cause cardiac apoptotic cell death.

53. A method as claimed in claim 49, wherein said agonist and said **antagonist** are administered to said patient following a surgical procedure having potential to result in cardiac apoptotic cell death.

54. A method as claimed in claim 49, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

55. A method as claimed in claim 49, wherein said patient is in need of said treatment due to acute myocardial infarction.

56. A method as claimed in claim 49, wherein said A3 agonist is selected from the group of compounds consisting of IB-MECA, Cl-IB-MECA, MRS 584, MRS 479, MRS 537, MRS 1340 and DBXMR and said A1 agonist is selected from the group of compounds listed in Table I.

57. A method as claimed in claim 49, wherein said apoptotic cell death is caused by a condition selected from the group consisting of idiopathic cardiomyopathy, cardiomyopathy induced by drugs, cardiomyopathy induced by chronic alcoholism, familial cardiomyopathy, viral myocarditis and cardiomyopathy induced by immunological rejection after heart transplantation.

58. A method for preventing or reducing apoptotic cell death mediated damage to the heart, in a patient in need thereof, comprising administering to said patient a binary conjugate acting as an agonist at the A3 **adenosine receptor** and an **antagonist** at the A2a **adenosine receptor**.

59. A method as claimed in claim 58, wherein said conjugate is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

60. A method as claimed in claim 58, wherein said conjugate is administered to said patient prior to a surgical procedure having potential to cause cardiac apoptotic cell death.

61. A method as claimed in claim 58, wherein said conjugate is

administered to said patient during a surgical procedure having potential to cause cardiac apoptotic cell death.

62. A method as claimed in claim 58, wherein said conjugate is administered to said patient following a surgical procedure having potential to result in cardiac apoptotic cell death.

63. A method as claimed in claim 58, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

64. A method as claimed in claim 58, wherein said patient is in need of said treatment due to acute myocardial infarction.

65. A method as claimed in claim 58, wherein said apoptotic cell death is caused by a condition selected from the group consisting of idiopathic cardiomyopathy, cardiomyopathy induced by drugs, cardiomyopathy induced by chronic alcoholism, familial cardiomyopathy, viral myocarditis and cardiomyopathy induced by immunological rejection after heart transplantation.

66. A method for preventing or reducing apoptotic cell death mediated damage to the heart, in a patient in need thereof, comprising administering to said patient a binary conjugate acting as an agonist at the A3 **adenosine receptor** and an agonist at the A1 **adenosine receptor**.

67. A method as claimed in claim 66, wherein said conjugate is delivered using an administration means selected from the group consisting of intravenous administration, oral administration and cardiac perfusion.

68. A method as claimed in claim 66, wherein said conjugate is administered to said patient prior to a surgical procedure having potential to cause cardiac apoptotic cell death.

69. A method as claimed in claim 66, wherein said conjugate is administered to said patient during a surgical procedure having potential to cause cardiac apoptotic cell death.

70. A method as claimed in claim 66, wherein said conjugate is administered to said patient following a surgical procedure having potential to result in cardiac apoptotic cell death.

71. A method as claimed in claim 66, wherein said patient is in need of said treatment due to an anginal condition selected from the group consisting of chronic stable angina, unstable angina, and post myocardial infarction angina.

72. A method as claimed in claim 66, wherein said patient is in need of said treatment due to acute myocardial infarction.

73. A method as claimed in claim 66, wherein said apoptotic cell death is caused by a condition selected from the group consisting of idiopathic cardiomyopathy, cardiomyopathy induced by drugs, cardiomyopathy induced by chronic alcoholism, familial cardiomyopathy, viral myocarditis and cardiomyopathy induced by immunological rejection after heart transplantation.

L14 ANSWER 6 OF 56 USPATFULL on STN
2003:127630 COMPOSITION, FORMULATIONS & METHOD FOR PREVENTION & TREATMENT OF DISEASES AND CONDITIONS ASSOCIATED WITH BRONCHOCONSTRICTION, ALLERGY(IES) & INFLAMMATION.
NYCE, JONATHAN W., PRINCETON, NJ, UNITED STATES
US 2003087845 A1 20030508
APPLICATION: US 1998-93972 A1 19980609 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A pharmaceutical composition, comprising a surfactant; and a nucleic acid which comprises an oligonucleotide (oligo) effective to alleviate bronchoconstriction, allegy (ies) or inflammation, the oligo being selected from the group consisting of oligonucleotides which are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of intron

and exon borders selected from the group consisting of the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNA(s) encoding an adenosine A_1, A_{2b} and A_3 receptors; anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of intron and exon borders selected from the group consisting of the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNA(s) encoding an adenosine A_1, A_{2b} and A_3 receptors, and consist of less than about 15% adenosine (A); combinations of the oligos; pharmaceutically acceptable salts of the oligos; and mixtures of the oligos, their combinations and their salts.

2. The composition of claim 1, wherein the oligo consists of up to about 10% A.

3. The composition of claim 2, wherein the oligo consists of up to about 5% A.

4. The composition of claim 3, wherein the oligo consists of up to about 3% A.

5. The composition of claim 4, wherein the oligo is A-free.

6. The composition of claim 1, wherein the target gene is selected from the group consisting of genomic flanking regions, target genes, sequences comprising an initiation codon, sequences comprising 2 or more G and/or C nucleotides, mRNAs and bridging sections thereof of the adenosine A_1 receptor.

7. The composition of claim 1, wherein the target gene is selected from the group consisting of genomic flanking regions, target genes, sequences comprising an initiation codon, sequences comprising 2 or more G and/or C nucleotides, mRNAs and bridging sections thereof of the adenosine A_{2a}, A_{2b} and A_3 receptor.

8. The composition of claim 1, wherein one A is substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have **antagonist** activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

9. The composition of claim 8, wherein all As are substituted by universal bases selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have **antagonist** activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

10. The composition of claim 8, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl.

11. The composition of claim 10, wherein the pyrimidines and purines are substituted at a position selected from the group consisting of positions 1, 2, 3, 4, 7 and 8.

12. The composition of claim 11, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula ##STR2## wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and

R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, $NH_{2\text{-alkylamino-ketoxyalkyloxy-aryl}}$ and mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl.

13. The composition of claim 12, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimlido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

14. The composition of claim 1, where a methylated cytosine (mC) is substituted for a C in at least one CpG dinucleotide if present in the oligo(s).

15. The composition of claim 1, wherein at least one mononucleotide linking phosphodiester residue of the anti-sense oligonucleotide(s) is selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, phosphorotrithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues and combinations thereof.

16. The composition of claim 15, wherein all phosphodiester residues are selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, phosphorotrithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues and combinations thereof.

17. The composition of claim 1, wherein the anti-sense oligonucleotide comprises about 7 to 60 mononucleotides.

18. The composition of claim 1, wherein the anti-sense oligonucleotide comprises SEQ ID NOS: 1, 3, 5, 7 and fragments 1-957 (SEQ. ID NO: 8-957) of SEQ. ID NO:7, and SEQ. ID NOS: 953-996.

19. The composition of claim 1, wherein the anti-sense oligonucleotide is linked to an agent selected from the group consisting of cell internalized or up-taken agent(s) and cell targeting agents.

20. The composition of claim 19, wherein the cell internalized or up taken agent is selected from the group consisting of transferrin, asialoglycoprotein and streptavidin.

21. The composition of claim 19, wherein the nucleic acid is linked to a vector.

22. The composition of claim 21, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

23. The composition of claim 1, wherein the surfactant is selected from the group consisting of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant protein and active fragments thereof, non-dipalmitoyl disaturated phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholin, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycero-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate, artificial lamellar bodies vehicles for surfactant components, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic ethylene and/or propylene oxide block copolymers, polyoxypropylene, polyoxyethylene, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100, ALEC, Exosurf, Survant and Atovaquone.

24. A cell, comprising the nucleic acid of claim 1.

25. The composition of claim 1, further comprising a carrier.

26. The composition of claim 25, wherein the carrier comprises a biologically acceptable carrier.

27. The composition of claim 26, wherein the carrier comprises a pharmaceutically or veterinarily acceptable carrier.

28. The composition of claim 25, wherein the carrier is selected from the group consisting of gaseous, liquid, solid carriers and mixtures thereof.

29. The composition of claim 25, further comprising an agent selected from the group consisting of other therapeutic agents, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, flavoring agents, propellants and preservatives.

30. The composition of claim 29, comprising the nucleic acid, the surfactant, a therapeutic agent and a pharmaceutically acceptable carrier.

31. The composition of claim 30, wherein the therapeutic agent is selected from the group consisting of other anti-adenosine A_1, A_{2b} and A_3 receptor agents, other anti-arrhythmic agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, adenosine and agents exhibiting adenosine agonist activity, analgesics, diuretics, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, Acute Respiratory Distress Syndrome (ARDS), ischemia, impeded and blocked respiration, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, antibody therapy agents and phototherapeutic agents.

32. The composition of claim 29, wherein the RNA inactivating agent comprises an enzyme.

33. The composition of claim 32, wherein the enzyme comprises a ribozyme.

34. The composition of claim 1, wherein the anti-sense oligonucleotide is present in an amount of about 0.01 to about 99.99 w/w of the composition.

35. The composition of claim 34, wherein the anti-sense oligonucleotide is present in an amount of about 1 to about 40 w/w of the composition.

36. A formulation, comprising the composition of claim 25, selected from the group consisting of systemic and topical formulations.

37. The formulation of claim 36, selected from the group consisting of oral, intrabuccal, intrapulmonary, rectal, intrauterine, intratumor, intracranial, nasal, intramuscular, subcutaneous, intravascular, intrathecal, inhalable, transdermal, intradermal, intracavitary, implantable, iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow release and enteric coating formulations.

38. The formulation of claim 37, which is an oral formulation, wherein the carrier is selected from the group consisting of solid and liquid carriers.

39. The formulation of claim 38, wherein the liquid carrier is selected from the group consisting of solutions, suspensions, and oil-in-water and water-in-oil emulsions.

40. The formulation of claim 38, which is selected from the group consisting of a powder, dragees, tablets, capsules, sprays, aerosols,

solutions, suspensions and emulsions.

41. The formulation of claim 36, which is a topical formulation, wherein the carrier is selected from the group consisting of creams, gels, ointments, sprays, aerosols, patches, solutions, suspensions and emulsions.

42. The formulation of claim 36, which is an injectable formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.

43. The formulation of claim 36, which is a rectal formulation in the form of a suppository.

44. The formulation of claim 36, which is a transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.

45. The formulation of claim 36, which is an iontophoretic transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions, and wherein the formulation further comprises a transdermal transport promoting agent.

46. An implantable capsule or cartridge, comprising the formulation of claim 44.

47. The formulation of claim 36, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.

48. The formulation of claim 36, wherein the carrier comprises a hydrophobic carrier.

49. The formulation of claim 48, wherein the carrier comprises lipid vesicles or particles.

50. The formulation of claim 49, wherein the vesicles comprise liposomes, and the particles comprise microcrystals.

51. The formulation of claim 50, wherein the vesicles comprise liposomes which comprise the anti-sense oligonucleotide.

52. The formulation of claim 49, wherein the vesicles comprise N-(1-[2, 3-dioleoxyloxi] propyl)-N,N,N-trimethyl-ammonium methylsulfate.

53. The formulation of claim 36, comprising a respirable or inhalable formulation.

54. The formulation of claim 53, comprising an aerosol.

55. The formulation of claim 36, in single or multiple unit form.

56. The formulation of claim 36, in bulk.

57. An anti-bronchoconstriction, anti-allergy and anti-inflammatory kit, comprising a delivery device; in separate containers, a surfactant or mixtures of surfactants, and a nucleic acid comprising an oligonucleotide (oligo) effective to alleviate bronchoconstriction, allergy (ies) or inflammation, the oligo being selected from the group consisting of oligonucleotides which are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of intron and exon borders selected from the group consisting of the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNA(s) encoding an adenosine A1, A2b and A3 receptors; anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of intron and exon borders selected from the group consisting of the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNA(s) encoding an adenosine A1, A2b and A3 receptors, and consist of less than about 15% adenosine (A); combinations of the

oligos; pharmaceutically acceptable salts of the oligos; and mixtures of the oligos, their combinations, their salts; and instructions for its use; and optionally an agent selected from the group consisting of other therapeutic and diagnostic agents, anti-oxidants, flavoring, fillers, volatile oils, dispersants, anti-oxidants, flavoring agents, propellants, preservatives, and buffering, RNA inactivating, cell-internalized or up-taken and coloring agents.

58. An anti-bronchoconstriction, anti-allergy and anti-inflammatory kit, comprising a delivery device; the composition of claim 1; and instructions for its use; and optionally and optionally an agent selected from the group consisting of other therapeutic and diagnostic agents, anti-oxidants, flavoring, fillers, volatile oils, dispersants, anti-oxidants, flavoring agents, propellants, preservatives, and buffering, RNA inactivating, cell-internalized or up-taken and coloring agents.

59. The kit of claim 58, wherein the delivery device comprises a nebulizer which delivers single metered doses of the formulation.

60. The kit of claim 59, wherein the nebulizer comprises an insufflator; and the composition is provided in a piercable or openable capsule or cartridge.

61. The kit of claim 59, wherein the delivery device comprises a pressurized inhaler; and the composition comprises a suspension, solution or dry formulation of the agent.

62. The kit of claim 61, comprising a surfactant, a nucleic acid and a therapeutic agent selected from the group consisting of other anti-adenosine A_1, A_{2b} and A_3 receptor **antagonists**, adenosine A_{2a} receptor stimulants, anti-inflammatory agents, anti-histaminic agents, anti-allergic agents, anti-bacterial, anti-vials, analgesics, kidney activity maintenance and restoration agents, anti-cancer agents, adenosine, blood pressure controlling agents, and diuretics.

63. The kit of claim 61, wherein the solvent is selected from the group consisting of organic solvents and organic solvents mixed with one or more co-solvents.

64. The kit of claim 57, wherein the composition is provided in a capsule or cartridge.

65. An in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to a subject the composition of claim 1, comprising an amount of the surfactant and of the nucleic acid effective to reach the target polynucleotide.

66. The method of claim 65, wherein the disease or condition is associated with bronchoconstriction, allergy and/or inflammation of the lung.

67. The method of claim 66, wherein the disease or condition is selected from the group consisting of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, Acute Respiratory Distress Syndrome (ARDS), renal damage or failure associated with ischemia and the administration of drugs and radioactive agents, side effects of adenosine and other anti-arrhythmic agents administered to treat arrhythmias and SupraVentricular Tachycardia (SVT) and to test cardiovascular function, ischemia, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate, metastatic cancer, and those which are treated with radiation, chemotherapeutic, antibody therapy and phototherapeutic agents.

68. The method of claim 65, wherein the composition is administered into the subject's respiratory system.

69. The method of claim 65, wherein the agent is effective to reduce the production or availability or to increase the degradation of the **adenosine receptor** mRNA or to reduce the amount of the **adenosine**

receptor.

70. The method of claim 65, wherein the agent is administered directly into the subject's lung (s).

71. The method of claim 65, wherein the agent is administered as a respirable aerosol.

72. The method of claim 65, wherein the disease or condition is associated with bronchoconstriction of the lung airways.

73. The method of claim 72, wherein the disease or condition is COPD, asthma, ARDS, side effects of adenosine administration or renal damage.

74. The method of claim 73, wherein the disease or condition is associated with inflammation.

75. The method of claim 74, wherein the therapeutic agent is selected from the group consisting of other adenosine A_1, A_{2b} and A_3 receptor inhibiting agents and adenosine A_{2a} receptor stimulating agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, antibody therapy agents, phototherapeutic agents, adenosine, and other anti-arrhythmic agents.

76. The method of claim 65, wherein the therapeutic agent is selected from the group consisting of anti-adenosine A_3 receptor agents.

77. The method of claim 65, wherein the disease or condition is associated with sepsis.

78. The method of claim 65, wherein the composition is administered by a topical or systemic route.

79. The method of claim 65, wherein the composition is administered orally, intracavitarily, intranasally, intraanally, intravaginally, intrauterally, intraarticularly, transdermally, intrabucally, intravenously, subcutaneously, intramuscularly, intravascularly, intratumorously, intraglandularly, intraocularly, intracranial, into an organ, intravascularly, intrathecally, intralymphatically, intraotically, by implantation, by inhalation, intradermally, intrapulmonarily, intraotically, by slow release, by sustained release and by a pump.

80. The method of claim 65, wherein the subject is a mammal.

81. The method of claim 80, wherein the mammals are selected from the group consisting of humans and animals.

82. The method of claim 81, wherein the mammal is a human.

83. The method of claim 81, wherein the subject is an animal.

84. The method of claim 65, wherein the anti-sense oligonucleotide is administered in amount of about 0.005 to about 150 mg/kg body weight.

85. The method of claim 84, wherein the anti-sense oligonucleotide is administered in an amount of about 0.01 to about 75 mg/kg body weight.

86. The method of claim 85, wherein the anti-sense oligonucleotide is administered in an amount of about 1 to 50 mg/kg body weight.

87. The method of claim 65, which is a prophylactic method.

88. The method of claim 65, which is a therapeutic method.

89. The method of claim 65, wherein the oligo is obtained by (a)

selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C; (b) obtaining a first oligonucleotide 4 to 60 nucleotide long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%; and (c) obtaining a second oligonucleotide 4 to 60 nucleotide long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an A base content of up to and including about 15%.

90. The method of claim 61, wherein the oligo consists of up to about 10% A.

91. The method of claim 90, wherein the oligo consists of up to about 5% A.

92. The method of claim 90, wherein the oligo consists of up to about 3% A.

93. The method of claim 93, wherein the oligo is A-free.

94. The method of claim 65, wherein the **adenosine receptor** target is selected from the group consisting of **adenosine receptor** genes and mRNAs and genomic flanking regions.

95. The method of claim 65, wherein at least one A is substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have **antagonist** activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

96. The method of claim 95, wherein all As are substituted by universal bases selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have **antagonist** activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A_1, A_{2b} and A_3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a} receptor.

97. The method of claim 95, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH_2, SH, SO, SO_2, SO_3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH_2, primary, secondary and tertiary amine, SH, SO, SO_2, SO_3, cycloalkyl, heterocycloalkyl and heteroaryl.

98. The method of claim 97, wherein the pyrimidines and purines are substituted at positions 1, 2, 3, 4, 7 and 8.

99. The method of claim 98, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula ##STR3## wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, $NH_{2\text{-alkylamino-ketoxyalkyloxy-aryl}}$ and mono and dialkylaminoalkyl-N-alkylamino-SO_2 aryl.

100. The method of claim 99, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

101. The method of claim 65, further comprising methylating at least one

cytosine (mC) if a CpG dinucleotide if present in the oligo(s).

102. The method of claim 65, further comprising substituting at least one mononucleotide linking phosphodiester residue of the anti-sense oligonucleotide(s) with a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), methyleneoxy (methylimino), 2'-O-methyl, phosphoramidate residues, and combinations thereof.

103. The method of claim 102, wherein all phosphodiester residues are substituted.

104. The method of claim 65, further comprising linking the anti-sense oligonucleotide to an agent selected from the group consisting of cell internalized and up-taken agent(s) and cell targeting agents.

105. The method of claim 104, wherein the cell internalized or up taken agent is selected from the group consisting of transferrin, asialoglycoprotein, and streptavidin.

106. The method of claim 104, wherein the cell targeting agent is a vector.

107. The method of claim 106, wherein the vector to which the agent is operatively linked is a prokaryotic or eukaryotic vector.

L14 ANSWER 7 OF 56 USPATFULL on STN
2003:113821 Methods and apparatus for acute or chronic delivery of substances or apparatus to extravascular treatment sites.
Makower, Joshua, Los Altos, CA, UNITED STATES
Lamson, Theodore C., Pleasonton, CA, UNITED STATES
Flaherty, J. Christopher, Topsfield, MA, UNITED STATES
Reggie, John A., Palo Alto, CA, UNITED STATES
Chang, John Y., Mountain View, CA, UNITED STATES
Catanese, Joseph, III, Redwood City, CA, UNITED STATES
Tholfsen, David R., San Francisco, CA, UNITED STATES
TransVascular, Inc., Menlo Park, CA, UNITED STATES, 94025 (U.S. corporation)
US 2003078562 A1 20030424
APPLICATION: US 2001-766502 A1 20010117 (9)
DOCUMENT TYPE: Utility; APPLICATION.

CLM What is claimed is:

1. A system for delivering substances or apparatus to an extravascular target site within the body of a human or veterinary patient, said system comprising: a. a vessel wall penetrating catheter that comprises i) a catheter body that is insertable into the vasculature of the patient and ii) a vessel wall penetrating member having a lumen extending longitudinally therethrough, said penetrating member being passable from the catheter body and through the wall of a blood vessel in which the catheter body is positioned; and, b. a delivery catheter having a lumen extending longitudinally therethrough, said delivery catheter being advanceable through the lumen of the vessel wall penetrating member to an extravascular target site; said vessel wall penetrating member being retractable into the catheter body of the vessel wall penetrating catheter and the vessel wall penetrating catheter being removeable from the patient's body such that the delivery catheter remains indwelling with the distal end of the delivery catheter located at the extravascular target site.

2. A system according to claim 1 wherein the vessel wall penetrating catheter further comprises iii) a guidance element useable by the operator to position the vessel wall penetrating catheter body within the vasculature of the patient such that when the vessel wall penetrating member is passed from the catheter body it will penetrate through the wall of the blood vessel in the direction of the intended extravascular target site.

3. A system according to claim 2 wherein the guidance element comprises an imaging apparatus.

4. A system according to claim 3 wherein the imaging apparatus is an

ultrasound imaging apparatus.

5. A system according to claim 2 wherein the guidance element comprises an imageable marker on the vessel wall penetrating catheter body.

6. A system according to claim 2 wherein the guidance element comprises the combination of an imaging apparatus and at least one imageable marker that is imageable by the imaging apparatus.

7. A system according to claim 2 wherein the guidance element comprises an emitter located on or in the catheter body, said emitter emitting a signal that is received by an extracorporeally situated signal-receiving apparatus.

8. A system according to claim 1 wherein the delivery catheter further comprises a matter blocking member for preventing cellular ingrowth and other matter from obstructing the lumen of the delivery catheter.

9. A system according to claim 8 wherein the delivery catheter has an outflow opening through which substances may pass out of the lumen of the delivery catheter and into the target location and wherein the matter blocking member comprises a selectively permeable barrier that allows desired substances to be infused in the distal direction through the outflow opening and to the target location but prevents cellular ingrowth and other matter from entering the lumen of the delivery catheter through said outflow opening.

10. A system according to claim 9 wherein the selectively permeable barrier is a balloon attached to the delivery catheter such that substances infused through the lumen of the delivery catheter collect within the balloon and subsequently diffuse outwardly through the balloon.

11. A system according to claim 8 wherein the matter blocking member comprises a stylet that is insertable into the lumen of the delivery catheter to block the entry of extraneous matter thereinto.

12. A system according to claim 11 wherein the stylet is removable from the lumen of the delivery catheter to permit delivery of a substance or apparatus through the delivery catheter.

13. A system according to claim 1 wherein the delivery catheter comprises: a first tube having a lumen and a sidewall in which an outflow aperture is formed; and, a second tube rotatably disposed in a coaxial position within the first tube, said second tube having a lumen, a closed distal end and a sidewall in which an opening is formed; the second tube being rotatably moveable between i) a blocking position wherein the side wall of the second tube substantially blocks the outflow aperture of the first tube to prevent cellular ingrowth and other matter from entering the lumen of the second tube and ii) an infusion position wherein the opening of the second tube is aligned with the outflow opening of the first tube such that a substance that is injected into the lumen of the second tube will flow through the opening of the second tube and through the outflow opening of the first tube.

14. A system according to claim 12 wherein a plurality of outflow apertures are formed in the sidewall of the first tube.

15. A system according to claim 1 wherein the delivery catheter comprises: a tube having a lumen and a sidewall in which an outflow aperture is formed; and, an obturator member disposed at least partially within the lumen of the tube, said obturator member being alternately disposable in i) a blocking position wherein the obturator substantially blocks the outflow aperture of the tube to prevent cellular ingrowth and other matter from entering the lumen of the tube and ii) an infusion position wherein the obturator does not substantially block the outflow apertures such that fluid may be injected through the lumen of the tube and out of the outflow aperture.

16. A system according to claim 15 wherein a plurality of outflow apertures are formed in the sidewall of the tube.

17. A system according to claim 15 wherein the obturator member is an inflatable balloon that assumes said blocking position when inflated and said infusion position when deflated.

18. A system according to claim 1 wherein the delivery catheter comprises an infusion lumen, a return lumen, an outflow aperture through which infused substances may flow out of the infusion lumen and a flow diverter, said flow diverter that is alternately deployable in i) an infusion position whereby substances infused through the infusion lumen will flow out of the outflow aperture and ii) a recirculation position whereby fluid infused through the infusion lumen will be recirculated back through the return lumen.

19. A system according to claim 1 wherein the delivery catheter comprises a pressure increasing outflow opening configured to cause an increase the pressure of fluids that are injected through the delivery catheter lumen and out of said pressure increasing outflow opening.

20. A system according to claim 19 wherein said pressure increasing outflow opening is formed in the side wall of the delivery catheter.

21. A system according to claim 20 wherein a plurality of pressure increasing outflow openings are formed in the side wall of the delivery catheter.

22. A system according to claim 1 wherein the delivery catheter further comprises an anchoring member for anchoring the catheter in a substantially fixed position within the patient's body.

23. A system according to claim 22 wherein the anchoring member is selected from the group of anchoring members consisting of: a hook; a barb; a permeable surface into which tissue may grow; an adhesive; and, combinations thereof.

24. A system according to claim 1 wherein the delivery catheter further comprises a backflow deterrent member for blocking backflow of substances that have been injected through the delivery catheter.

25. A system according to claim 24 wherein said backflow deterrent member comprises a backflow barrier rib formed on the delivery catheter.

26. A system according to claim 25 wherein said backflow barrier comprises an inflatable balloon on the delivery catheter.

27. A system according to claim 25 wherein said backflow barrier comprises a raised projection formed on the exterior of the delivery catheter.

28. A system according to claim 27 wherein the raised projection comprises an annular rib formed about the outer surface of the delivery catheter

29. A system according to claim 24 wherein the backflow deterrent comprises a sealant that is implanted prior to or concurrently with removal of the delivery catheter so as to prevent the injected substance from bacflowing through the tract from which the delivery catheter is removed.

30. A system according to claim 29 wherein the sealant comprises a quantity of a flowable sealant injected into the tract upon removal of the delivery catheter.

31. A system according to claim 29 wherein the sealant comprises a detachable sealing member.

32. A system according to claim 31 wherein the detachable sealing member is formed of biodegradable material.

33. A system according to claim 32 wherein the sealing member is a collagen sponge.

34. A system according to claim 32 wherein the sealing member is a hydrogel sponge.

35. A system according to claim 1 wherein at least a portion of the delivery catheter is coated with an adhesive.

36. A system according to claim 1 wherein an anti-microbial substance is

disposed on at least a portion of the delivery catheter.

37. A system according to claim 1 wherein an anti-coagulant substance is disposed on at least a portion of the delivery catheter.

38. A system according to claim 1 further comprising apparatus for creating a pocket within tissue adjacent to the delivery catheter such that when a substance or apparatus is introduced through the delivery catheter it will be received within said pocket.

39. A system according to claim 38 wherein the apparatus for creating a pocket comprises an energy emitting member that emits energy into adjacent tissue to create said pocket.

40. A system according to claim 39 wherein the energy emitting apparatus is a radiofrequency electrode.

41. A system according to claim 39 wherein the energy emitting apparatus is a laser.

42. A system according to claim 38 wherein the apparatus for creating a pocket comprises a nozzle through which a stream of fluid may be injected to create the pocket in adjacent tissue.

43. A system according to claim 38 wherein the apparatus for creating a pocket comprises an expandable cage which, when expanded, creates said pocket.

44. A system according to claim 1 further in combination with an infusion apparatus for infusing a substance through the delivery catheter.

45. A system according to claim 44 wherein said infusion apparatus is a syringe.

46. A system according to claim 44 wherein said infusion apparatus is a pump.

47. A system according to claim 44 wherein said infusion apparatus is a reservoir positioned for gravity drainage of the substance through the delivery catheter.

48. A system according to claim 44 wherein said infusion apparatus further comprises a quantity of a substance for infusion through the delivery catheter.

49. A system according to claim 48 wherein the substance is a drug.

50. A system according to claim 49 wherein the drug is selected from the group consisting of: thrombolytics, platelet inhibitors, anti-restenotic agents, beta adrenergic blockers, ion channel **antagonists**, positive or negative ionotropic agents, anti-arrhythmics and combinations thereof.

51. A system according to claim 48 wherein the substance is a protein.

52. A system according to claim 48 wherein the substance is an angiogenic substance.

53. A system according to claim 51 wherein the angiogenic substance is selected from the group consisting of vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF) or scatter factor, heparin combined with an **adenosine receptor** agonist, and combinations thereof.

54. A system according to claim 48 wherein the substance comprises cells.

55. A system according to claim 54 wherein the substance comprises progenator cells for a type of cell that is desired to be formed at the target site.

56. A system according to claim 55 wherein said substance comprises myoblasts to form cardiac muscle cells.

57. A system according to claim 56 wherein said cells are selected from the group consisting of stem cells, progenator cells, myoblasts, myocytes, secretory cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes, cloned cells, cells grown in cell culture, genetically modified cells, and combinations thereof.

58. A system according to claim 48 wherein the substance is a gene.

59. A system according to claim 48 wherein the substance comprises a gene and a vector for facilitating entry of the gene into locations within cells at which the gene will have a desired effect on the cells.

60. A system according to claim 59 wherein the vector is a virus.

61. A method for delivering a substance or apparatus to an extravascular target site within the body of a human or veterinary patient, said method comprising the steps of: (A) providing a vessel wall penetrating catheter that is insertable into the vasculature of the patient, said vessel wall penetrating catheter having a penetrating member that is advanceable through the wall of a blood vessel in which the catheter body is positioned, said vessel wall penetrating member having a lumen extending longitudinally therethrough; (B) inserting the vessel wall penetrating catheter into the vasculature of the patient; (C) positioning the vessel wall penetrating catheter within the vasculature of the patient such that the penetrator, when advanced, will pass through the wall of a blood vessel to a location near the target site; (D) advancing the penetrator through the wall of a blood vessel and to a location near the target site; (E) advancing through the lumen of the penetrator and to the target site, a second apparatus selected from the group consisting of: i. an elongate delivery catheter having a lumen through which a substance may be injected or withdrawn; ii. an elongate member that comprises a therapeutic apparatus operative to deliver a therapy to the target site; iii. an elongate member that comprises an information obtaining apparatus operative to obtain information from the target site; and, iv. possible combinations thereof.

62. A method according to claim 61 wherein the vessel wall penetrating catheter further comprises a guidance element useable by the operator to position the vessel wall penetrating catheter body within the vasculature of the patient such that when the vessel wall penetrating member is passed from the catheter body it will penetrate through the wall of the blood vessel in the direction of the intended extravascular target site, and wherein Step C further comprises using said guidance element to position the vessel wall penetrating catheter body within the vasculature of the patient such that when the vessel wall penetrating member is passed from the catheter body it will penetrate through the wall of the blood vessel in the direction of the intended extravascular target site.

63. A method according to claim 62 wherein the guidance element comprises an imaging apparatus and wherein Step C further comprises using the imaging apparatus to image at least the target site and using such image to guide the positioning of the vessel wall penetrating catheter.

64. A method according to claim 63 wherein the imaging apparatus is an ultrasound imaging apparatus and the image used in Step C is an ultrasound image.

65. A method according to claim 62 wherein the guidance element comprises indicia that indicates the path that will be followed by the penetrator when it is subsequently advanced from the catheter penetrating catheter and wherein Step C further comprises obtaining an image of the imageable marker and using such image to guide the positioning of the vessel wall penetrating catheter.

66. A method according to claim 65 wherein the guidance element comprises the combination of an imaging apparatus and at least one imageable marker on the vessel wall penetrating catheter, and wherein Step C further comprises using the imaging apparatus to obtain an image of at least the imageable marker and using that image to guide the positioning of the vessel wall penetrating catheter.

67. A method according to claim 66 wherein the imageable marker provides an indication of the direction in which the penetrator will advance and

wherein Step C further comprises imaging of the imageable marker to obtain an indication of the direction in which the penetrator will advance and using said indication to rotationally orient and position the vessel wall penetrating catheter such that subsequent advancement of the penetrator will cause the penetrator to travel in the direction of the target site.

68. A method according to claim 62 wherein the guidance element comprises an emitter located on or in the catheter body, said emitter emitting a signal that is received by an extracorporeally situated signal-receiving apparatus and wherein Step C further comprises using an extracorporeally situated signal-receiving apparatus to receive a signal from the emitter and to thereby guide the placement of the vessel wall penetrating catheter.

69. A method according to claim 61 wherein the second apparatus comprises an elongate delivery catheter having a lumen through which a substance may be delivered and wherein the method further comprises the step of: (F) delivering a substance through the delivery catheter to the target site.

70. A method according to claim 69 wherein the delivery catheter is a microcatheter having an outer diameter of less than 0.5 mm.

71. A method according to claim 69 wherein the delivery catheter further comprises a matter blocking member for preventing cellular ingrowth and other matter from obstructing the lumen of the delivery catheter and wherein the method further comprises the step of: using said matter blocking member to prevent cellular ingrowth and other matter from obstructing the lumen of the delivery catheter at least during times when no substance is being infused through the delivery catheter.

72. A method according to claim 71 wherein the delivery catheter has an outflow opening through which substances may pass out of the lumen of the delivery catheter and into the target location and wherein the matter blocking member comprises a selectively permeable barrier that allows desired substances to be infused in the distal direction through the outflow opening and to the target location but prevents cellular ingrowth and other matter from entering the lumen of the delivery catheter through said outflow opening, and wherein the method further comprises the step of: infusing a substance in the distal direction through the delivery catheter and, thereafter, allowing the substance to pass outwardly through the selectively permeable barrier.

73. A method according to claim 71 wherein the selectively permeable barrier comprises a balloon attached to the delivery catheter and wherein the method further comprises the step of: infusing a substance the distal direction through the delivery catheter such that the substance collects within the balloon and subsequently diffuses outwardly through the balloon.

74. A method according to claim 71 wherein the matter blocking member comprises a stylet that is insertable into the lumen of the delivery catheter to block cellular ingrowth and other matter from entering thereinto and wherein the method further comprises the step of: inserting the stylet into the lumen of the delivery catheter at least at times when no substance is being infused through said lumen, thereby blocking the entry of cellular ingrowth and other matter into the delivery catheter lumen.

75. A method according to claim 74 wherein the stylet is removable from the lumen of the delivery catheter to permit delivery of a substance or apparatus through the delivery catheter and wherein the method further comprises the step of: removing the stylet from the delivery catheter lumen when it is desired to deliver a substance or apparatus through the delivery catheter lumen.

76. A method according to claim 69 wherein the delivery catheter comprises: a first tube having a lumen and a sidewall in which an outflow aperture is formed; and, a second tube rotatably disposed in a coaxial position within the first tube, said second tube having a lumen, a closed distal end and a sidewall in which an opening is formed; the second tube being rotatably moveable between i) a blocking position wherein the side wall of the second tube substantially blocks the outflow aperture of the first tube to prevent cellular ingrowth and

other matter from entering the lumen of the second tube and ii) a delivery position wherein the opening of the second tube is aligned with the outflow opening of the first tube such that a substance that is injected into the lumen of the second tube will flow through the opening of the second tube and through the outflow opening of the first tube, and wherein said method further comprises the steps of: placing the second tube in the blocking position when no substance or apparatus is being delivered through the delivery catheter; and, placing the second tube in the delivery position when a substance or apparatus is being delivered through the delivery catheter.

77. A method according to claim 71 wherein the delivery catheter comprises: a tube having a lumen and a sidewall in which an outflow aperture is formed; and, an obturator member disposed at least partially within the lumen of the tube, said obturator member being alternately disposable in i) a blocking position wherein the obturator substantially blocks the outflow aperture of the tube to prevent cellular ingrowth and other matter from entering the lumen of the tube and ii) a delivery position wherein the obturator does not substantially block the outflow apertures such that fluid may be injected through the lumen of the tube and out of the outflow aperture; and wherein the method further comprises the steps of: placing the obturator in the blocking position when no substance or apparatus is being delivered through the delivery catheter; and, placing the obturator in the delivery position when a substance or apparatus is being delivered through the delivery catheter.

78. A method according to claim 77 wherein the obturator member is an inflatable balloon that assumes said blocking position when inflated and said infusion position when deflated, and wherein the step of placing the obturator in the blocking position comprises inflating the balloon and the step of placing the obturator in the delivery position comprises deflating the balloon.

79. A method according to claim 69 wherein the delivery catheter comprises a delivery lumen, a return lumen, an aperture through which substances or apparatus delivered through the delivery lumen may pass out of the delivery catheter and a flow diverter, said flow diverter that is alternately deployable in i) a delivery position whereby substances or apparatus may be delivered through the delivery catheter lumen and out of the aperture and ii) a recirculation position whereby fluid infused through the delivery lumen will be recirculated back through the return lumen and wherein the method further comprises the steps of: placing the diverter in the delivery position when it is desired to deliver a substance or apparatus through the delivery lumen and out of the aperture; and, placing the diverter in the recirculation position and infusing a fluid through the delivery lumen and back through the recirculation lumen, when no substance or apparatus is being delivered through the delivery lumen.

80. A method according to claim 69 wherein the delivery catheter comprises a pressure increasing outflow opening configured to cause an increase the pressure of substances that are injected through the delivery catheter lumen and out of said pressure increasing outflow opening, and wherein the method further comprises the step of: delivering a substance through the delivery catheter and out of the outflow opening such that the pressure of the substance increases as it flows out of the outflow opening.

81. A method according to claim 69 wherein the substance delivered in Step F is a therapeutic substance.

82. A method according to claim 69 wherein the substance delivered in Step F is a agent that provides an enhanced image of the target site.

83. A method according to claim 69 wherein the substance delivered in Step F is a traceable substance that may be used to determine the rate at which the substance distributes away from or is otherwise inactivated at the target site or other pharmacokinetic or biodistributive parameters or variables.

84. A method according to claim 81 wherein the therapeutic substance is selected from the group consisting of: a drug, a protein, cells, an angiogenic substance, a myogenic substance, a neurogenic substance, a gene, a gene therapy composition, genetic material in combination with a

vector for delivering the genetic material into locations within cells at which the genetic material will have a desired effect on the cells;

85. A method according to claim 81 wherein the method is carried out to improve perfusion of an ischemic target site and where the therapeutic substance delivered in Step F comprises is an angiogenic agent that increases vascularity of the ischemic target site.

86. A method according to claim 85 wherein the angiogenic agent delivered in Step F is selected from the group of angiogenic agents consisting of vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF) or scatter factor, heparin combined with an **adenosine receptor** agonist, nerve cell growth factor (NGF), and combinations thereof.

87. A method according to claim 81 wherein the therapeutic substance delivered in Step F comprises cells.

88. A method according to claim 87 wherein said cells are selected from the group consisting of stem cells, progenator cells, myoblasts, myocytes, secretory cells, pancreatic islet cells, dopamine secreting cells, endothelial cells, hepatocytes, cloned cells, cells grown in cell culture, genetically modified cells, and combinations thereof.

89. A method according to claim 87 wherein the method is carried out to treat a condition characterized by a deficiency of a type of cell within the patient's body and wherein the type of cell that is deficient matures in situ from stem cells, and wherein the therapeutic substance delivered in Step F comprises stem cells of a type that mature into the deficient cell type.

90. A method according to claim 89 wherein the method is carried out to treat a condition characterized by a lack of living myocytes iin or near the target site and wherein the therapeutic substance delivered in Step F comprises myocytes.

91. A method according to claim 89 wherein the method is carried out to treat parkinsonism, the target site comprises the substantia nigra of the patient's brain and wherein the therapeutic substance delivered in Step F comprises dopamine secreting cells which when implanted will increase dopamine in the substantia nigra.

92. A method according to claim 91 wherein the dopamine secreting cells comprise fetal dopamine secreting cells.

93. A method according to claim 89 wherein the method is carried out to treat diabetes, the target site comprises the patient's pancreas, and wherein the therapeutic substance delivered in Step F comprises insulin secreting cells which, when implanted, will increase insulin production by the patient's pancreas.

94. A method according to claim 93 wherein the insulin secreting cells comprise pancreatic β islet cells.

95. A method according to claim 81 wherein the method is carried out to treat a neurogenerative disorder and wherein the substance delivered comprises nerve cells.

96. A method according to claim 81 wherein the method is carried out to treat a neurogenerative disorder and wherein the substance delivered comprises a substance that facilitates nerve growth.

97. A method according to claim 96 wherein the substance delivered is selected from the group consisting of: glial cell line-derived neurotropic factor (GDNF), nerve growth factor, neuro-immunophilin ligand, poly ADP-Ribose polymerase, and combinations thereof.

98. A method according to claim 81 wherein the therapeutic substance comprises a gene in combination with a vector for facilitating entry of the gene into locations within cells in which the gene will have a desired therapeutic effect.

99. A method according to claim 98 wherein the vector is a virus.

100. A method according to claim 61 wherein the second apparatus further comprises an anchoring member for holding the second apparatus in a substantially fixed position within the patient's body and wherein the method further comprises the step of: (F) causing the anchoring apparatus to hold the second apparatus in a substantially fixed position within the patient's body.

101. A method according to claim 100 wherein the anchoring member is selected from the group of anchoring members consisting of: a hook; a barb; a permeable surface into which tissue may grow; an adhesive; and, combinations thereof; and wherein Step F comprises causing the anchoring apparatus to engage tissue adjacent thereto so as to hold the second apparatus in said substantially fixed position.

102. A method according to claim 61 wherein the second apparatus is a delivery catheter, wherein the delivery catheter further comprises a backflow deterrent for blocking backflow of substances that have been injected through the delivery catheter and wherein the method further comprises the step of: causing the backflow deterrent to deter backflow of a substance that has been infused through the delivery catheter to the target site.

103. A method according to claim 102 wherein the backflow deterrent comprises a backflow barrier rib formed on the delivery catheter and wherein the step of causing the backflow deterrent to deter backflow is carried out by positioning the backflow deterrent rib so that is acts as a barrier to the unwanted backflow.

104. A method according to claim 103 wherein said backflow barrier comprises an inflatable balloon on the delivery catheter and wherein the step causing the backflow deterrent to deter backflow is carried out by inflating the balloon.

105. A method according to claim 102 wherein said backflow deterrent comprises a raised projection formed on the exterior of the delivery catheter and wherein the step of causing the backflow deterrent to deter backflow is carried out by positioning the raised projection so that is acts as a barrier to the unwanted backflow.

106. A method according to claim 105 wherein the raised projection comprises an annular rib formed about the outer surface of the delivery catheter

107. A method according to claim 102 wherein the backflow deterrent comprises a sealant which, when implanted in the penetration tract through which the delivery catheter was advanced, will prevent the substance from bacflowing through that tract, and wherein Step F of the method comprises implanting the sealant into the penetration tract.

108. A method according to claim 107 wherein the sealant is implanted into the tract prior to removal of the delivery catheter.

109. A method according to claim 107 wherein the sealant is implanted into the tract prior concurrently with removal of the delivery catheter.

110. A method according to claim 107 wherein the sealant comprises a quantity of a flowable sealant and wherein the step of implanting the sealant into the penetration tract comprises injecting the flowable sealant into the penetration tract.

111. A method according to claim 110 wherein the injecting of the flowable sealant into the penetration tract comprises injecting the flowable sealant through the delivery catheter.

112. A method according to claim 107 wherein the sealant comprises a detachable sealing member and wherein Step F comprises introducing the sealing member into the penetration tract and thereafter detaching the sealing member such that it will remain in the penetration tract after the delivery catheter has been removed.

113. A method according to claim 112 wherein the detachable sealing member comprises biodegradable material and wherein Step F comprises introducing the biodegradable member into the penetration tract and thereafter detaching the biodegradable member such that it will remain in the penetration tract after the delivery catheter has been removed.

114. A method according to claim 112 wherein the sealing member is a collagen sponge and wherein Step F comprises introducing the collagen sponge into the penetration tract and thereafter detaching the collagen sponge such that it will remain in the penetration tract after the delivery catheter has been removed.

115. A method according to claim 112 wherein the sealing member is a hydrogel material and wherein Step F comprises introducing the hydrogel material into the penetration tract and thereafter detaching the hydrogel material such that it will remain in the penetration tract after the delivery catheter has been removed.

116. A method according to claim 61 wherein at least a portion of the second apparatus is coated with an adhesive and wherein the method further comprises the step of: (F) causing the adhesive to adhere to adjacent tissue thereby deterring movement of the second apparatus.

117. A method according to claim 61 wherein an anti-microbial substance is disposed on at least a portion of the second apparatus and wherein the method further comprises the step of: (F) causing the anti-microbail substance to deter microbial growth in the area surrounding the portion of the second apparatus on which the anti-microbial substance is disposed.

118. A method according to claim 61 wherein an anti-coagulant substance is disposed on at least a portion of the second apparatus and wherein the method further comprises the step of: (F) causing the anti-coagulant substance to deter coagulative processes in the area surrounding the portion of the second apparatus on which the anti-coagulant substance is disposed.

119. A method according to claim 69 wherein the apparatus further comprises a tissue pocket creating apparatus and wherein the method further comprises the step of: using the tissue pocket creating apparatus to create a pocket within tissue adjacent to the delivery catheter such that when a substance or apparatus is introduced through the delivery catheter it will be received within said pocket

120. A method according to claim 119 wherein the tissue pocket creating apparatus comprises an energy emitting member and wherein the step of using the tissue pocket creating apparatus comprises causing the tissue pocket creating apparatus to emit energy into adjacent tissue to create a tissue pocket therein.

121. A method according to claim 120 wherein the energy emitting apparatus is a radiofrequency electrode and wherein the step of using the tissue pocket creating apparatus comprises causing the electrode to emit energy of a magnitude and duration sufficient to create the tissue pocket.

122. A method according to claim 120 wherein the energy emitting apparatus is a laser.

123. A method according to claim 119 wherein the tissue pocket creating apparatus comprises a nozzle through which a stream of fluid may be injected and wherein the step of using the tissue pocket creating apparatus comprises injecting fluid through the nozzle to create the pocket in adjacent tissue.

124. A method according to claim 119 wherein the tissue pocket creating apparatus comprises an expandable cage and wherein the step of using the tissue pocket creating apparatus comprises expanding the cage to create the pocket in adjacent tissue.

125. A method according to claim 61 wherein the second apparatus is an elongate member that comprises a therapeutic apparatus operative to deliver a therapy to the target site and wherein the method further comprises the step of: (F) using the therapeutic apparatus to deliver therapy to the target site.

126. A system for delivery of a substance to a target site located a spaced distance from a blood vessel within the body of a human or animal patient, said system comprising: a vessel wall penetrating catheter that has a vessel wall penetrator advanceable therefrom, said vessel

wall penetrating catheter being insertable into the vasculature and positionable in the blood vessel near the target site and said penetrator being thereafter advanceable from the catheter and trough the wall of the blood vessel in the direction of the target site; a delivery catheter that is advanceable through the penetrator and to the target site, said delivery catheter being of sufficient length and constructed such that, after the delivery catheter has been advanced through the penetrator and to the target site, the penetrator may be retracted into the vessel wall penetrating catheter and the vessel wall penetrating catheter may be removed, leaving the delivery catheter in place such that the delivery catheter extends through the patient's vasculature into the blood vessel near the target site, outwardly through the wall of the blood vessel and to the target site.

127. A system according to claim 126 wherein the delivery catheter comprises a hub member that is a) not attached to the proximal end of the delivery catheter while the vessel wall penetrating catheter is being withdrawn and removed and b) attached to the proximal end of the delivery catheter after the vessel wall penetrating catheter has been withdrawn and removed.

128. A system according to claim 126 wherein the delivery catheter further comprises at least one anchoring element for holding the delivery at the target site.

129. A system according to claim 127 wherein the delivery catheter further comprises a barrier for deterring substances injected through the delivery catheter from backflowing around the delivery catheter through the tissue tract through which the delivery catheter extends from the blood vessel to the target site.

130. A system according to claim 126 wherein the delivery catheter further comprises apparatus for preventing cellular ingrowth and other matter from obstructing the lumen of the delivery catheter.

131. A system according to claim 126 wherein the vessel wall penetrating catheter further comprises a guidance element that facilitates positioning and orientation of the vessel wall penetrating catheter within the blood vessel such that, then the penetrator is subsequently advanced from the vessel wall penetrating catheter, the penetrator will travel substantially toward the target site.

132. A method for delivery of substances or apparatus to a target site located a spaced distance from a blood vessel within the body of a human or animal patient, said method comprising the steps of: (A) Inserting a vessel wall penetrating catheter into the vasculature of the patient, said vessel wall penetrating catheter having a penetrator advanceable therefrom; (B) positioning the vessel wall penetrating catheter in the blood vessel near the target site; (C) advancing the penetrator from the vessel wall penetrating catheter and through the wall of the blood in the direction of the target site; (D) advancing a delivery catheter through the penetrator and to the target site; (E) retracting the penetrator into the vessel wall penetrating catheter; and, (F) withdrawing and removing the vessel wall penetrating catheter, leaving the delivery catheter indwelling such that it extends through the patient's vasculature into the blood vessel near the target site, outwardly through the wall of the blood vessel and to the target site.

133. A method according to claim 132 wherein the delivery catheter comprises a hub member that is a) not attached to the proximal end of the delivery catheter while the vessel wall penetrating catheter is being withdrawn and removed and b) attached to the proximal end of the delivery catheter after the vessel wall penetrating catheter has been withdrawn and removed, and wherein the method further comprises the steps of: causing the hub member to be detached from the delivery catheter while the vessel wall penetrating catheter is being withdrawn and removed in Step F; and, causing the hub member to be attached to the proximal end of the delivery catheter after the vessel wall penetrating catheter has been withdrawn and removed in Step F.

134. A method according to claim 132 wherein the delivery catheter further comprises at least one anchoring element for holding the delivery at the target site and wherein the method further comprises: causing the anchoring element to hold the delivery catheter at the target site at least after Step F has been performed.

135. A method according to claim 132 wherein the delivery catheter further comprises a barrier for deterring substances injected through the delivery catheter from backflowing around the delivery catheter through the tissue tract through which the delivery catheter extends from the blood vessel to the target site and wherein the method further comprises: causing the barrier to deter substances injected through the delivery catheter from backflowing around the delivery catheter through the tissue tract through which the delivery catheter extends from the blood vessel to the target site

136. A system according to claim 132 wherein the delivery catheter further comprises apparatus for preventing cellular ingrowth and other matter from obstructing the lumen of the delivery catheter and wherein the method further comprises the step of: causing the apparatus for preventing cellular ingrowth and other matter from obstructing the lumen of the delivery catheter to prevent cellular ingrowth or other matter from obstructing the lumen of the delivery catheter.

137. A system according to claim 126 wherein the vessel wall penetrating catheter further comprises a guidance element that facilitates positioning and orientation of the vessel wall penetrating catheter within the blood vessel such that, then the penetrator is subsequently advanced from the vessel wall penetrating catheter, the penetrator will travel substantially toward the target site and wherein the method further comprises the step of: using the guidance element to position and orient the vessel wall penetrating catheter in the blood vessel prior to performance of Step C such that when Step C is subsequently performed, the penetrator will travel through the blood vessel wall substantially in the direction of the target site

L14 ANSWER 8 OF 56 USPATFULL on STN
2003:106796 Compounds specific to adenosine A3 receptor and uses thereof.
Castelhano, Arlindo L., New City, NY, UNITED STATES
McKibben, Bryan, White Plains, NY, UNITED STATES
Witter, David J., Putman Valley, NY, UNITED STATES
US 2003073708 A1 20030417
APPLICATION: US 2001-6405 A1 20011130 (10)
PRIORITY: US 2000-250748P 20001201 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound having the structure: ##STR277##

2. A method for inhibiting the activity of an A_3 **adenosine receptor** in a cell, which comprises contacting the cell with a compound of claim 1.

3. The method of claim 2, wherein the compound is an **antagonist** of the A_3 **adenosine receptor**.

4. The method of claim 2, wherein the cell is human cell.

5. The method of claim 4, wherein the compound is an **antagonist** of A_3 **adenosine receptors**.

6. A method of treating damage to the eye of a subject which comprises administering to the subject a composition comprising a therapeutically effective amount of the compound of claim 1.

7. The method of claim 6, wherein the damage comprises retinal or optic nerve head damage.

8. A therapy for glaucoma, comprising administering to a subject a therapeutically effective amount of the compound of claim 1.

9. A combination therapy for glaucoma, comprising the compound of claim 1, and one or more compounds selected from the group consisting of beta adrenoceptor **antagonists**, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandins and prostaglandin receptor agonists, angiotensin converting enzyme (ACE) inhibitors, AMPA receptor **antagonists**, 5-HT agonists, angiogenesis inhibitors, NMDA **antagonists**, renin inhibitors, cannabinoid receptor agonists, angiotensin receptor **antagonists**, hydrochlorothiazide

(HCTZ), somatostatin agonists, glucocorticoid **antagonists**, mast cell degranulation inhibitors, alpha-adrenergic receptor blockers, alpha-2 adrenoceptor **antagonists**, thromboxane A2 mimetics, protein kinase inhibitors, prostaglandin F derivatives, prostaglandin-2 alpha **antagonists**, dopamine D1 and 5-HT2 agonists, nitric-oxide-releasing agents, 5-HT 2 **antagonists**, cyclooxygenase inhibitors, inosine, dopamine D2 receptor and alpha 2 adrenoceptor agonists, dopamine D1 receptor **antagonist** and D2 receptor agonists, vasopressin receptor **antagonists**, endothelin **antagonists**, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) and related analogs and prodrugs, thyroid hormone receptor ligands, muscarinic M1 agonists, sodium channel blockers, mixed-action ion channel blockers, beta adrenoceptor **antagonist** and PGF2 alpha agonist combinations, guanylate cyclase activators, nitrovasodilators, endothelin receptor modulators, ethacrynic acid, other phenoxyacetic acid analogs, actin disrupters, calcium channel blockers and neuroprotective agents.

10. A combination therapy for glaucoma, comprising the compound of claim 1, and one or more compounds selected from the group consisting of beta adrenoceptor **antagonists**, alpha-2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists and prostaglandin receptor agonists.

11. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

12. A packaged pharmaceutical composition for treating a disease associated with A_3 **adenosine receptor** in a subject, comprising: (a) a container holding a therapeutically effective amount of the compound of claim 1; and (b) instructions for using said compound for treating said disease in a subject.

13. A method of making a composition which comprises the compound of claim 1, the method comprising admixing the compound of claim 1 with a suitable carrier.

14. A pharmaceutically acceptable salt of the compound of claim 1.

15. The pharmaceutically acceptable salt of claim 14, wherein the pharmaceutically acceptable salt contains an anion selected from the group consisting of maleic, fumaric, tartaric, acetate, phosphate and mesylate.

L14 ANSWER 9 OF 56 USPATFULL on STN
2003:85872 Composition and treatment method for brain and spinal cord injuries.
Wang, Yanming, Malden, MA, UNITED STATES
US 2003059476 A1 20030327
APPLICATION: US 2001-962009 A1 20010924 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A neuroprotective medicament composition for protecting the central nervous system of a mammal comprising a solution of an amphipathic lipid in an oil.

2. A neuroprotective medicament composition for protecting the central nervous system of a mammal consisting essentially of a solution of an amphipathic lipid in an oil.

3. A neuroprotective composition according to claim 1 or 2 wherein the oil is selected from the group consisting of hydrocarbon oils, silicone oil, and Vitamin E.

4. A neuroprotective composition according to claim 3 wherein the treatment oil is selected from the group consisting of Vitamin E, soybean oil, mineral oil, cod liver oil, and peanut oil.

5. A neuroprotective composition according to claim 1 or 2 wherein the amphipathic lipid is selected from the group consisting of, phospholipids, phosphoglycerides, sphingomyelin, glycolipids, cholesterol, cholesterol hemisuccinate, sphingolipids, and cerebrosides.

6. A composition according to claim 5 wherein the amphipathic lipid is

lecithin

7. A method for protecting Central Nervous System tissue in need of such protection in a mammal, comprising the steps of: a) Withdrawing a volume of cerebrospinal fluid from the subarachnoid space in the region where protection is needed for Central Nervous System tissue, b) Injecting a volume of a treatment solution approximately equal to the volume of cerebrospinal fluid withdrawn into said subarachnoid spaces, and c) Administering a CSF production-suppressing agent in an amount effective to reduce or stop said CSF production.

8. A method for protecting Central Nervous System tissue in need of such protection according to claim 7 wherein said treatment solution is a solution comprising an amphipathic lipid in oil.

9. A method for protecting Central Nervous System tissue in need of such protection according to claim 7 wherein said treatment solution is a solution consisting essentially of an amphipathic lipid in oil.

10. A method for protecting Central Nervous System tissue in need of such protection according to claim 8 wherein said treatment solution comprises about 1 gram of lecithin per 100 ml. of soybean oil.

11. A method for protecting central nervous system tissue in a mammal according to claim 7 comprising the added step of administering a cellular energy supplying substance.

12. A method for protecting central nervous system tissue in a mammal according to claim 7 comprising the added step of administering an agent that reduces cellular energy requirements.

13. A method for protecting central nervous system tissue according to claim 7 wherein said treatment solution further comprises an osmotic dehydrant.

14. A method for protecting central nervous system tissue according to claim 7 wherein said CSF suppression agent is furosemide.

15. A method for reducing the effects of central nervous system ischemia in a mammal comprising the steps of: Withdrawing a volume of cerebrospinal fluid from the subarachnoid space of the central nervous system of the mammal and Injecting a volume of a treatment solution approximately equal to the volume of the cerebrospinal fluid withdrawn into said subarachnoid spaces.

16. A method for reducing the effects of central nervous system ischemia in a mammal according to claim 15 wherein said treatment solution comprises an amphipathic lipid in oil.

17. A method for treating a central nervous system injury in a mammal requiring such treatment comprising: Withdrawing a volume of cerebrospinal fluid from the subarachnoid space of the central nervous system of the mammal, and Injecting a volume of a treatment solution approximately equal to the volume of the cerebrospinal fluid withdrawn into said subarachnoid spaces.

18. A method for treating a central nervous system injury in a mammal according to claim 17 wherein said treatment solution comprises an amphipathic lipid in oil.

19. A method for screening agents for neuroprotective effect comprising the steps of withdrawing cerebrospinal fluid from the subarachnoid spaces of a living test subject and administering treatment oil comprising an amphipathic lipid in an oil with a proposed neuroprotective agent to said living test subject and determining the effectiveness of said neuroprotective agent.

20. A method for treating a central nervous system injury in a mammal requiring such treatment comprising: Withdrawing a volume of cerebrospinal fluid from the subarachnoid space of the central nervous system of the mammal, Injecting a volume of a treatment solution comprising an amphipathic lipid in oil approximately equal to the volume of the cerebrospinal fluid withdrawn into said subarachnoid spaces, and administering an effective amount of a neuroprotective agent to mammal whereby the therapeutic window of said neuroprotective agent is

lengthened.

21. A method for treating a central nervous system injury in a mammal requiring such treatment comprising: Withdrawing a volume of cerebrospinal fluid from the subarachnoid space of the central nervous system of the mammal, Injecting a volume of a treatment solution comprising an amphipathic lipid in oil approximately equal to the volume of the cerebrospinal fluid withdrawn into said subarachnoid spaces, and administering an effective amount of a neuroprotective agent selected from the group consisting of: calcium channel blockers, calcium chelators, potassium channel blockers, free radical scavengers, antioxidants, GABA agonists, GABA receptor **antagonists**, glutamate **antagonists**, NMDA **antagonists**, NMDA channel blockers, glycine site **antagonists**, polyamine site **antagonists**, **adenosine receptor antagonists**, growth factors, Glial cell line derived neurotrophic factor (GDNF), brain derived neurotrophic factor, insulin like growth factor, leukocyte adhesion inhibitors, nitric oxide inhibitors, opiod **antagonists**, Serotonin agonists, sodium channel blockers, potassium channel openers, anti-inflamatory agents, and protein kinase inhibitors to said mammal whereby the therapeutic window of said neuroprotective agent is lengthened.

22. A method for treating stroke in a mammal requiring such treatment comprising: Withdrawing a volume of cerebrospinal fluid from the subarachnoid space of the central nervous system of the mammal, injecting a volume of a treatment solution comprising an amphipathic lipid in oil approximately equal to the volume of the cerebrospinal fluid withdrawn into said subarachnoid spaces, and administering a thrombolytic agent to said mammal in an amount effective to restore blood flow to central nervous system tissue.

23. A method according to claim 22 wherein said thrombolytic agent includes recombinant tissue plasminogen activator (rt-PA).

L14 ANSWER 10 OF 56 USPATFULL on STN
2003:65412 Compounds specific to adenosine A1 receptors and uses thereof.
Castelhano, Arlindo L., New City, NY, UNITED STATES
McKibben, Bryan, White Plains, NY, UNITED STATES
Witter, David J., Putman Valley, NY, UNITED STATES
US 2003045536 A1 20030306
APPLICATION: US 2001-280 A1 20011130 (10)
PRIORITY: US 2000-250895P 20001201 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound having the structure: ##STR284## wherein R_{1NR2} together form a ring having the structure: ##STR285## or R_1 is H and R_2 is: ##STR286## R_5 is H, or substituted or unsubstituted alkyl or alkylaryl.

2. The compound of claim 1, having the structure: ##STR287##

3. The compound of claim 1, having the structure: ##STR288##

4. The compound of claim 1, having the structure: ##STR289##

5. The compound of claim 1, having the structure: ##STR290##

6. The compound of claim 1, having the structure: ##STR291##

7. The compound of claim 1, having the structure: ##STR292##

8. The compound of claim 1, having the structure: ##STR293##

9. The compound of claim 1, having the structure: ##STR294##

10. The compound of claim 1, having the structure: ##STR295##

11. The compound of claim 1, having the structure: ##STR296##

12. The compound of claim 1, having the structure: ##STR297##

13. The compound of claim 1, having the structure: ##STR298##

14. The compound of claim 1, having the structure: ##STR299##

15. The compound of claim 1, having the structure: ##STR300##

16. The compound of claim 1, having the structure: ##STR301##

17. The compound of claim 1, having the structure: ##STR302##

19. A method for treating a disease associated with A_1 **adenosine receptor** in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claim 1.

20. The method of claim 19, wherein the subject is a mammal.

21. The method of claim 20, wherein the mammal is a human.

22. The method of claim 19, wherein said A_1 **adenosine receptor** is associated with cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, branchoconstriction, neutropil chemotaxis, reflux condition, or ulcerative condition.

23. A water-soluble prodrug of the compound of claim 1, wherein the water-soluble prodrug is metabolized in vivo to produce an active drug which selectively inhibits A_1 **adenosine receptor**.

24. The prodrug of claim 23, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

25. A pharmaceutical composition comprising the prodrug of claim 23 and a pharmaceutically acceptable carrier.

26. A method for inhibiting the activity of an Al **adenosine receptor** in a cell, which comprises contacting the cell with a compound of claim 1.

27. The method of claim 26, wherein the compound is an **antagonist** of the A_1 **adenosine receptor**.

28. The method of claim 26, wherein the cell is human cell.

29. The method of claim 28 wherein the compound is an **antagonist** of A_1 **adenosine receptors**.

30. The method of claim 19, wherein said disease is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

31. The method of claim 30, wherein the subject is a human.

32. The method of claim 31, wherein said compound is an **antagonist** of A_1 **adenosine receptors**.

33. A combination therapy for asthma, comprising the compound of claim 1, and a steroid, β_2 agonist, glucocorticoid, lucotriene **antagonist**, or anticolinergic agonist.

34. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

35. The method of claim 30, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

36. The pharmaceutical composition of claim 34, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

37. The pharmaceutical composition of claim 34, wherein said pharmaceutical composition is a systemic formulation.

38. The pharmaceutical composition of claim 34, wherein said pharmaceutical composition is a surgical irrigating solution.

39. A packaged pharmaceutical composition for treating a disease associated with A1 **adenosine receptor** in a subject, comprising: (a) a container holding a therapeutically effective amount of the compound of claim 1; and (b) instructions for using said compound for treating said disease in a subject.

40. A pharmaceutically acceptable salt of the compound of claim 1.

41. The pharmaceutically acceptable salt of claim 40, wherein the pharmaceutically acceptable salt of the compound of claims 6, 8, 12, 15, or 16 contains a cation selected from the group consisting of sodium, calcium and ammonium.

42. The method of claim 19, wherein the A_1 **adenosine receptor** is associated with congestive heart failure.

L14 ANSWER 11 OF 56 USPATFULL on STN
2003:60224 Methods for reducing intraocular pressure using A3 **adenosine receptor antagonists**.
Civan, Mortimer M., Wynnewood, PA, United States
Stone, Richard A., Havertown, PA, United States
Mitchell, Claire H., Philadelphia, PA, United States
Jacobson, Kenneth A., Silver Springs, MD, United States
Trustees of the University of Pennsylvania, The Center for Technology Transfer, Philadelphia, PA, United States (U.S. corporation)
US 6528516 B1 20030304
WO 2000003741 20000127
APPLICATION: US 2001-743744 20010504 (9)
WO 1999-US16211 19990715
PRIORITY: US 1999-122965P 19990303 (60)
US 1998-93097P 19980716 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for reducing intraocular pressure in an individual with an ocular disorder, comprising the step of administering to said individual an effective intraocular pressure-reducing amount of a pharmaceutical composition comprising an A_3 subtype **adenosine receptor antagonist**.

2. The method of claim 1, wherein said A_3 subtype receptor **antagonist** is a dihydropyridine, pyridine, pyridinium salt or triazoloquinazoline.

3. The method of claim 1, wherein said As subtype receptor **antagonist** is selected from the group consisting of MRS-1097, MRS-1191, MRS-1220, MRS-1523 and MRS-1649.

4. The method of claim 1, wherein said pharmaceutical composition is administered topically, systemically or orally.

5. The method of claim 1, wherein said pharmaceutical composition is an ointment, gel or eye drops.

6. The method of claim 1, wherein said ocular disorder is glaucoma.

7. A method for reducing intraocular pressure in an individual with an ocular disorder, comprising the step of administering to said individual an effective intraocular pressure-reducing amount of a pharmaceutical composition comprising an antiestrogen.

8. The method of claim 7, wherein said antiestrogen is tamoxifen.

9. The method of claim 7, wherein said pharmaceutical composition is administered topically, systemically or orally.

10. The method of claim 7, wherein said pharmaceutical composition is ointment, gel or eye drops.

11. The method of claim 7, wherein said ocular disorder is glaucoma.

12. A method for reducing intraocular pressure in an individual with an ocular disorder, comprising the step of administering to said individual an effective intraocular pressure-reducing amount of a pharmaceutical composition comprising a calmodulin **antagonist**.

13. The method of claim 12, wherein said calmodulin **antagonist** is trifluoperazine.

14. The method of claim 12, wherein said pharmaceutical composition is administered topically, systemically or orally.

15. The method of claim 12, wherein said pharmaceutical composition is ointment, gel or eye drops.

16. The method of claim 12, wherein said ocular disorder is glaucoma.

17. A method for reducing intraocular pressure in an individual with an ocular disorder, comprising the step of administering to said individual an effective intraocular pressure-reducing amount of a pharmaceutical composition comprising a prodrug which is converted into a A_3 subtype **adenosine receptor antagonist** after said administering step.

L14 ANSWER 12 OF 56 USPATFULL on STN
2003:51587 Compounds specific to adenosine A2a receptor and uses thereof.
Castelhano, Arlindo L., New City, NY, UNITED STATES
McKibben, Bryan, White Plains, NY, UNITED STATES
Witter, David J., Putman Valley, NY, UNITED STATES
US 2003036545 A1 20030220
APPLICATION: US 2000-728607 A1 20001204 (9)
PRIORITY: US 1999-169037P 19991202 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A compound having the structure: ##STR226## wherein NR_{1R2} is a substituted or unsubstituted 4-8 membered ring; wherein Ar is a substituted or unsubstituted four to six membered ring; wherein R_4 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $--C(R_8)(R_9)XR_6$, wherein X is O, S, or NR_7, wherein R_8 and R_9 are each independently H or alkyl, wherein R_6 and R_7 are each independently alkyl or cycloalkyl, or R_6, R_7 and the nitrogen together form a substituted or unsubstituted ring of between 4 and 7 members. wherein R_5 is H, alkyl, substituted alkyl, or cycloalkyl; with the proviso that NR_{1R2} is not 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, or 3-aminocarbonylmethyl pyrrolidino; with the proviso that NR_{1R2} is 4-hydroxymethyl piperadino only when Ar is 4-pyridyl.

2. The compound of claim 1, wherein Ar is phenyl, pyrrole, thiophene, furan, thiazole, pyridine.

3. The compound of claim 1, having the structure: ##STR227## wherein m is 0, 1, 2, or 3; wherein R_A and R_B are each independently be H, $--OH$, $--CH_{2OH}$, $--CH_{2CH2OH}$, $--C(.dbd.O)NH_2$, a heteroatom, or $--C(.dbd.O)NR_{3R3}'$; wherein R_3 is aryl, substituted aryl, or heteroaryl; wherein R_3' is alkyl, or $XR_3"$, wherein X is O, or N and R" is substituted alkyl or aryl.

4. The compound of claim 1, having the structure: ##STR228## wherein m is 0, 1, 2, or 3; wherein Y is O, S, or NR, wherein R is R_A or R_B; wherein R_A and R_B are each independently be H, $--OH$, $--CH_{2OH}$, $--CH_{2CH2OH}$, $--C(.dbd.O)NNH_2$, a heteroatom, or $--C(.dbd.O)NR_{3R3}^1$; wherein R_3 is aryl, substituted aryl, or heteroaryl; wherein R_3' is alkyl, or $XR_3"$, wherein X is O, or N and R" is substituted alkyl or aryl.

5. The compound of claim 1, wherein R_{1R2N} is (D)-2-aminocarbonyl pyrrolidino, (D)-2-hydroxymethyl pyrrolidino, (D)-2-hydroxymethyl- trans-4-hydroxy pyrrolidino, piperazino, or 3-hydroxymethyl piperadino.

6. The compound of claim 1, having the structure: ##STR229##

7. The compound of claim 1, having the structure: ##STR230##

8. The compound of claim 1, having the structure: ##STR231##

9. The compound of claim 1, having the structure: ##STR232##

10. The compound of claim 1, having the structure: ##STR233##

11. The compound of claim 1, having the structure: ##STR234##

12. The compound of claim 1, having the structure: ##STR235##

13. The compound of claim 1, having the structure: ##STR236##

14. The compound of claim 11, having the structure: ##STR237##

15. The compound of claim 11, having the structure: ##STR238##

16. A compound having the structure(V): ##STR239## wherein R is H, or methyl.

17. The compound of claim 16, having the structure: ##STR240##

18. The compound of claim 16, having the structure: ##STR241##

19. A method for treating a disease associated with A_{2a} **adenosine receptor** in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claims 1, or 16.

20. The method of claim 19, wherein the subject is a mammal.

21. The method of claim 20, wherein the mammal is a human.

22. The method of claim 21, wherein said A_{2a} **adenosine receptor** is associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, senile dementia, or Parkinson's disease.

23. The method of claim 19, wherein the compound treats said diseases by stimulating adenylate cyclase.

24. A water-soluble prodrug of the compound of claims 1, or 16, wherein said water-soluble prodrug that is metabolized in vito to an active drug which selectively inhibit A_{2a} **adenosine receptor**.

25. The prodrug of claim 24, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

26. A pharmaceutical composition comprising the prodrug of claim 24 and a pharmaceutically acceptable carrier.

27. A method for inhibiting the activity of an A_{2a} **adenosine receptor** in a cell, which comprises contacting said cell with a compound of claims 1, or 16.

28. The method of claim 27, wherein the compound is an **antagonist** of said A_{2a} **adenosine receptor**.

29. The method of claim 28, wherein the cell is a human cell.

30. The method of claim 28, wherein the compound is an **antagonist** of A_{2a} **adenosine receptors**.

31. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claims 1, or 16 and a pharmaceutically acceptable carrier.

32. The pharmaceutical composition of claim 31, wherein said therapeutically effective amount is effective to treat Parkinson's disease and diseases associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, or senile dementia.

33. The pharmaceutical composition of claim 31, wherein said pharmaceutical composition is an ophthalmic formulation.

34. The pharmaceutical composition of claim 31, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

35. The pharmaceutical composition of claim 31, wherein said pharmaceutical composition is a systemic formulation.

36. The pharmaceutical composition of claim 31, wherein said pharmaceutical composition is a surgical irrigating solution.

37. A combination therapy for Parkinson's disease, comprising the compounds of claims 1 or 16, and any of the dopamine enhancers.

38. A combinational therapy for cancer, comprising the compound of claims 1 or 16, and any of the cytotoxic agents.

39. A combinational therapy for glaucoma, comprising the compound of claims 1 or 16, and a prostaglandin agonist, a muscrinic agonist, or a β-2 **antagonist.**

40. A packaged pharmaceutical composition for treating a disease associated with A_{2a} **adenosine receptor** in a subject, comprising: (a) a container holding a therapeutically effective amount of the compound of claims 1, or 16; and (b) instructions for using said compound for treating said disease in a subject.

41. A method of preparing the compound of claim 1, comprising the steps of a) ##STR242## wherein P is a removable protecting group; b) treating the product of step a) under cyclization conditions to provide ##STR243## c) treating the product of step b) under suitable conditions to provide ##STR244## d) treating the chlorinated product of step c) with NR_{1R2} to provide ##STR245## wherein NR_{1R2} is a substituted or unsubstituted 4-8 membered ring; wherein Ar is a substituted or unsubstituted four to six membered ring, wherein R_4 is H, alkyl, substituted alkyl, aryl, arylalkyl, amino, substituted aryl, wherein said substituted alkyl is $--C(R_8)(R_9)XR_6$, wherein X is O, S, or NR_7, wherein R_8 and R_9 are each independently H or alkyl, wherein R_6 and R_7 are each independently alkyl or cycloalkyl, or R_6, R_7 and the nitrogen together form a substituted or unsubstituted ring of between 4 and 7 members. wherein R_5 is H, alkyl, substituted alkyl, or cycloalkyl; with the proviso that NR_{1R2} is not 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino;

42. A method of preparing the compound of claim 16, comprising the steps of a) ##STR246## wherein P is a removable protecting group; b) treating the product of step a) under cyclization conditions to provide ##STR247## c) treating the product of step b) under suitable conditions to provide ##STR248## d) treating the chlorinated product of step c) first with dimethylamine and formaldehyde, then with N-methyl benzylamine and finally with NH_{2R1} to provide ##STR249## wherein R_1 is acetomido ethyl; wherein Ar is 4-pyridyl; wherein R is H, or methyl; wherein R_5 is N-methyl-N-benzyl aminomethyl.

L14 ANSWER 13 OF 56 USPATFULL on STN
2002:295072 Use of purinergic receptor modulators and related reagents.
Cockayne, Debra Ann, San Jose, CA, UNITED STATES
Ford, Anthony P.D.W., Mountain View, CA, UNITED STATES
Zhu, Quan-Ming, Sunnyvale, CA, UNITED STATES
Lachnit, Wilhelm G., Burlingame, CA, UNITED STATES
Malmberg, Annika B., Palo Alto, CA, UNITED STATES
US 2002165117 A1 20021107
APPLICATION: US 2001-783067 A1 20010213 (9)
PRIORITY: US 2000-182445P 20000215 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating a subject having a disease state associated with a genitourinary or pain disorder comprising administering to the animal an effective amount of a purinoreceptor modulator.

2. The method of claim 1, wherein the genitourinary disorder is an overactive bladder.

3. The method of claim 1, wherein the genitourinary disorder is outlet

obstruction.

4. The method of claim 1, wherein the genitourinary disorder is outlet insufficiency.

5. The method of claim 1, wherein the genitourinary disorder is pelvic hypersensitivity.

6. The method of claim 1, wherein the pain disorder is peripheral pain, inflammatory pain, or tissue injury pain.

7. The method of claim 1, wherein the purinoreceptor modulator is a **P2X receptor** complex modulator.

8. The method of claim 7, wherein the **P2X receptor** complex comprises at least one $P2X_3$ receptor subunit.

9. The method of claim 7, wherein the **P2X receptor** complex modulator is an **antagonist**.

10. The method of claim 7, wherein the **P2X receptor** complex modulator is an agonist.

11. The method of claim 1, wherein the subject is a mammal.

12. The method of claim 11, wherein the mammal is a human.

13. A transgenic animal containing an altered allele for the gene that naturally encodes and expresses a functional $P2X_3$ receptor subunit.

14. The transgenic animal of claim 13, wherein the altered allele is a non-functional allele.

15. The transgenic animal of claim 13, wherein the transgenic animal is a knockout (KO) animal.

16. The KO animal of claim 15, wherein the phenotype of the KO animal relative to a wild-type control animal comprises: a) an increase in urinary bladder capacity; b) a lower frequency of urine voiding; c) a larger voided volume; and d) no significant change in cystometric pressure.

17. The KO animal of claim 15, wherein the phenotype of the KO animal relative to a wild-type control animal comprises: a) attenuated nociception in response to injection of ATP; or b) attenuated nociception in response to injection of formalin.

18. The KO animal of claim 15, wherein the animal is a mouse.

19. A method for selecting a potential therapeutic compound for use in the treatment of a disease state associated with a genitourinary disorder comprising: a) administering the compound to a wild-type animal or an animal having a disease state associated with a genitourinary disorder; b) measuring the resulting phenotype of wild-type animal or the animal having the disease state; and c) comparing the resulting pheontype of the wild-type animal or the animal having the disease state to the phenotype of the knockout animal of claim 16.

20. A method for selecting a potential therapeutic compound for use in the treatment of a disease state associated with a pain disorder comprising: d) administering the compound to a wild-type animal or an animal having a disease state associated with a pain disorder; e) measuring the resulting phenotype of wild-type animal or the animal having the disease state; and f) comparing the resulting pheontype of the wild-type animal or the animal having the disease state to the phenotype of the knockout animal of claim 17.

L14 ANSWER 14 OF 56 USPATFULL on STN
2002:287552 Methods, pharmaceutical formulations and kits for identification of subjects at risk for cancer and for the prevention of cancer in at- risk subjects.
Neely, Constance F., Raleigh, NC, UNITED STATES
US 2002160415 A1 20021031

APPLICATION: US 2000-569394 A1 20000512 (9)
PRIORITY: US 1999-134276P 19990514 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A method of determining a subject's risk for developing cancer, comprising: obtaining a sample of diagnostic cells from a subject; and then determining a measure of cytotoxicity of the diagnostic cells for target cancer cells, the measure of cytotoxicity correlating negatively with the risk for developing cancer.

2. The method according to claim 1, wherein the measure of cytotoxicity is determined by evaluating the affinity of the diagnostic cells for at least one A_1 **adenosine receptor** ligand.

3. The method according to claim 1, wherein the measure of cytotoxicity is determined by evaluating the number of A_1 **adenosine receptors** on the diagnostic cells.

4. The method according to claim 1, wherein the measure of cytotoxicity is determined by evaluating the affinity of the diagnostic cells for MCP-1 protein.

5. The method according to claim 1, further comprising the steps of: priming the diagnostic cells by contacting the diagnostic cells with a priming agent in an amount sufficient to prime the diagnostic cells; and activating the diagnostic cells by contacting the diagnostic cells with an activating agent in an amount sufficient to induce cytotoxicity in the diagnostic cells; wherein the priming and activating steps occur prior to determining the measure of cytotoxicity of the diagnostic cells for target cancer cells.

6. The method according to claim 5, wherein the measure of cytotoxicity is determined by evaluating the release of cytotoxins from the diagnostic cells.

7. The method according to claim 5, wherein the cytotoxin is tumor necrosis factor α (TNF-α).

8. The method according to claim 5, wherein the measure of cytotoxicity is determined by evaluating the percentage of target cancer cells killed by the diagnostic cells.

9. The method according to claim 1, wherein the diagnostic cells are selected from the group consisting of macrophages, monocytes, promonocytes and peripheral blood stem cells.

10. The method according to claim 5, wherein the activating agent is an A_1 **adenosine receptor** agonist.

11. The method according to claim 5, wherein the activating agent is conjugated to a lipid.

12. The method according to claim 5, wherein said priming agent is selected from the group consisting of phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon gamma (IFNτ), granulocyte-macrophage colony stimulating factor (GMCSF), and f-met-leu-phe (fMLP).

13. The method according to claim 5, wherein said priming agent is conjugated to a lipid.

14. The method according to claim 1, wherein said subject is human.

15. The method according to claim 5, wherein said measure of cytotoxicity is determined by evaluating the affinity of the diagnostic cells for at least one A_1 **adenosine receptor** ligand and by evaluating the percentage of target cancer cells killed by the diagnostic cells.

16. A method of preventing cancer in a subject at risk for developing cancer, comprising administering to the subject a priming agent in an amount effective to prime cells of the of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

17. The method according to claim 16, wherein the priming agent is conjugated to a lipid.

18. The method according to claim 16, further comprising administering to the subject an activating agent in an amount effective to activate cells of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

19. The method according to claim 18, wherein the activating agent is conjugated to a lipid.

20. The method according to claim 18, wherein the priming agent and the activating agent are formulated together in a liposomal formulation.

21. The method of preventing cancer in a subject at risk of developing cancer, comprising increasing the expression of A_1 **adenosine receptors** in the cells of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

22. The method according to claim 21, wherein expression of A_1 **adenosine receptors** in the cells of the subject is increased by transfecting the cells with a cDNA encoding the human A_1 **adenosine receptor**.

23. The method according to claim 21, wherein expression of A_1 **adenosine receptors** in the cells of the subject is increased by administering to the cells a compound selected from the group consisting of cisplatin, daunorubicin, doxorubicin, mitoxantrone, dexamethasone, and carbamazepine, in an amount effective to increase the expression of A_1 **adenosine receptors** in the cells of the subject.

24. The method according to claim 21, wherein expression of A_1 **adenosine receptors** in the cells of the subject is increased by administering to the cells an **adenosine receptor antagonist** in an amount effective to increase the expression of A_1 **adenosine receptors** in the cells of the subject.

25. The method according to claim 24, wherein the **adenosine receptor antagonist** is theophylline.

26. A method of preventing cancer in a subject at risk of developing cancer, comprising increasing the affinity of the cells of the subject for A_1 **adenosine receptor** ligands, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

27. The method according to claim 26, comprising administering to the cells of the subject an allosteric enhancer for A_1 **adenosine receptors** in an amount sufficient to increase the affinity of the cells of the subject for A_1 **adenosine receptor** ligands.

28. A pharmaceutical liposomal formulation for the prevention of cancer in a subject determined to be at risk for developing cancer, comprising: a priming agent and an activating agent encapsulated in liposomes.

29. The pharmaceutical liposomal formulation according to claim 28, wherein the priming agent is selected from the group consisting of phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon gamma (IFNγ), granulocyte-macrophagecolony stimulating factor (GMCSF), and f-met-leu-phe (fMLP).

30. The pharmaceutical liposomal formulation according to claim 28, wherein the activating agent is an A_1 **adenosine receptor** agonist.

31. The pharmaceutical liposomal formulation according to claim 28, wherein the formulation is a timed-release formulation, and wherein the priming agent is released prior to the release of the activating agent.

32. A diagnostic kit for determining a subject's risk for developing cancer comprising: at least one reagent for determining the cytotoxicity of diagnostic cells of the subject; and printed

instructions for assessing the subject's risk for developing cancer, wherein the at least one reagent and the printed instructions are packaged together in a container.

33. The diagnostic kit according to claim 32, wherein the at least one reagent for determining the cytotoxicity of the diagnostic cells of the subject is selected from the group consisting of ligands for A_1 **adenosine receptors**, ligands for MCP-1 protein, and ligands for annexins.

34. The diagnostic kit according to claim 32, wherein the kit comprises at least one priming agent and at least one activating agent.

35. The diagnostic kit according to claim 34, wherein the priming agent is selected from the group consisting of phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon gamma (IFNτ), granulocyte-macrophage colony stimulating factor (GMCSF), and f-met-leu-phe (fMLP).

36. The kit according to claim 34, wherein the priming agent is conjugated to a lipid.

37. The kit according to claim 34, wherein the amount of priming agent in the kit is sufficient to prime diagnostic cells of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

38. The kit according to claim 34, wherein the amount of activating agent in the kit is sufficient to activate diagnostic cells of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

39. The kit according to claim 34, wherein the activating agent is an A_1 **adenosine receptor antagonist**.

40. The kit according to claim 34, wherein the activating agent is conjugated to a lipid.

41. The kit according to claim 34, wherein the priming agent and the activating agent are formulated together in a liposomal formulation.

42. A kit for preventing cancer in a subject determined to be at-risk for the development of cancer, comprising: at least one reagent selected from the group consisting of reagents for increasing A_1 **adenosine receptor** expression in macrophages, monocytes, peripheral blood stem cells and promonocytes, reagents for increasing binding of A_1 **adenosine receptor** ligands to macrophages, monocytes, peripheral blood stem cells and promonocytes, reagents for increasing binding of MCP-1 protein for macrophages, monocytes, peripheral blood stem cells and promonocytes, priming agents and activating agents; and printed instructions for administering the at least one reagent to the cells of the subject, wherein the at least one reagent and the printed instructions are packaged together in a container.

43. The kit according to claim 42, wherein the kit comprises at least one priming agent and at least one activating agent.

44. The kit according to claim 43, wherein the priming agent is selected from the group consisting of phorbol myristoyl acetate (PMA), lipopolysaccharide (LPS), interferon gamma (IFNτ), granulocyte-macrophage colony stimulating factor (GMCSF), and f-met-leu-phe (fMLP).

45. The kit according to claim 43, wherein the priming agent is conjugated to a lipid.

46. The kit according to claim 43, wherein the amount of priming agent in the kit is sufficient to prime cells of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

47. The kit according to claim 43, wherein the amount of activating agent is sufficient to activate cells of the subject, wherein the cells are selected from the group consisting of monocytes, macrophages, promonocytes and peripheral blood stem cells.

48. The according to claim 43, wherein the activating agent is an A_1 **adenosine receptor antagonist**.

49. The kit according to claim 43, wherein the activating agent is conjugated to a lipid.

50. The kit according to claim 43, wherein the priming agent and the activating agent are formulated together in a liposomal formulation.

L14 ANSWER 15 OF 56 USPATFULL on STN
2002:251929 **Adenosine receptor**.
Hedrick, Joseph A., South River, NJ, UNITED STATES
Lachowicz, Jean E., Berkeley Heights, NJ, UNITED STATES
Wang, Wei, Palo Alto, CA, UNITED STATES
Gustafson, Eric L., Annandale, NJ, UNITED STATES
US 2002137887 A1 20020926
APPLICATION: US 2001-765034 A1 20010117 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An isolated polypeptide comprising at least 12 contiguous residues of the amino acid sequence of SEQ ID NO: 2.

2. An isolated polypeptide comprising the amino acid sequence defined by SEQ ID NO: 2 or a adenosine binding fragment thereof.

3. An antibody which specifically binds to the polypeptide of claim 2.

4. An isolated or recombinant nucleic acid encoding the polypeptide of claim 1.

5. A recombinant vector comprising the nucleic acid of claim 4.

6. A host cell comprising the recombinant vector of claim 5.

7. A method for making a polypeptide comprising culturing a host cell of claim 6 under conditions in which the nucleic acid is expressed.

8. The method of claim 7 in which the polypeptide is isolated from the culture.

9. An isolated or recombinant nucleic acid selected from the group consisting of: (a) a nucleic acid encoding a polypeptide comprising the amino acid sequence defined by SEQ ID NO: 2; (b) a nucleic acid that hybridizes under moderately stringent conditions to the nucleic acid of (a) and encodes a polypeptide that (i) binds adenosine and (ii) is at least 80% identical to a polypeptide encoded by the nucleic acid of (a); and (c) a nucleic acid that, due to the degeneracy of the genetic code, encodes a polypeptide encoded by a nucleic acid of (a) or (b).

10. A recombinant vector comprising the nucleic acid of claim 9.

11. A host cell comprising the recombinant vector of claim 10.

12. A method for making a polypeptide comprising culturing a host cell of claim 11 under conditions in which the nucleic acid is expressed.

13. The method of claim 12 in which the receptor is isolated from the culture.

14. A method for identifying an agonist or **antagonist** of a mammalian **adenosine receptor**, comprising: (a) contacting the polypeptide of claim 2 in the presence of a known amount of labeled adenosine or a surrogate thereof with a sample to be tested for the presence of a adenosine agonist or **antagonist**; and (b) measuring the amount of labeled adenosine or surrogate specifically bound to the polypeptide; whereby a adenosine agonist or **antagonist** in the sample is identified by measuring substantially reduced binding of the labeled adenosine or surrogate to the polypeptide, compared to what would be measured in the absence of such agonist or **antagonist**.

15. The method of claim 14 which further comprises: (c) contacting the polypeptide in the presence of a known amount of labeled adenosine or a

surrogate thereof with a compound identified as a adenosine agonist or **antagonist** in steps (a) and (b); and (d) measuring the amount of labeled adenosine or surrogate bound to the polypeptide; whereby a adenosine agonist or **antagonist** specific for a mammalian **adenosine receptor** is identified by measuring substantially undiminished binding of the labeled adenosine or surrogate to the polypeptide, compared to what would be measured in the absence of such agonist or **antagonist**.

16. A method for identifying an agonist or **antagonist** of a mammalian **adenosine receptor** comprising: (a) contacting cells expressing the polypeptide of claim 2, in the presence of a known amount of adenosine or surrogate thereof with a sample to be tested for the presence of a mammalian **adenosine receptor** agonist or **antagonist**; and (b) measuring at least one cellular function modulated by the binding of a ligand to said polypeptide; whereby a mammalian **adenosine receptor** agonist or **antagonist** in the sample is identified by measuring its effect on said cellular function compared to what would be measured in the absence of such agonist or **antagonist**.

17. An agonist or **antagonist** of a mammalian **adenosine receptor** identified by the method of claim 14.

18. An agonist or **antagonist** of a mammalian **adenosine receptor** identified by the method of claim 16.

19. A method for treating an adenosine-mediated medical condition comprising administering to a mammal afflicted with a medical condition caused or mediated by adenosine, an effective amount of an agonist or **antagonist** of the polypeptide of claim 2.

20. A method for measuring expression of a mammalian **adenosine receptor** gene in a biological sample comprising the steps of: (a) isolating messenger RNA from the sample; (b) reverse transcribing the messenger RNA into cDNA; (c) performing PCR on the cDNA using oligonucleotide primers derived from a nucleic acid encoding the polypeptide of claim 2; and (d) quantifying the amount of PCR product.

L14 ANSWER 16 OF 56 USPATFULL on STN
2002:214247 Modulation of GSK-3beta activity and its different uses.
Fishman, Pnina, Herzliya, ISRAEL
Khalili, Kamel, Merion, PA, UNITED STATES
US 2002115635 A1 20020822
APPLICATION: US 2001-788477 A1 20010221 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for a therapeutic treatment, comprising administering to a subject in need an effective amount of an active agent for achieving a therapeutic effect, the therapeutic effect conprises modulating GSK-3β activity in cells and said active agent is selected from the group consisting of an adenosine A1 receptor ligand (A1RL) and A2 **adenosine receptor** ligand (A2RL), an adenosine A3 receptor ligand (A3RL) and a combination of the same.

2. The method of claim 1, wherein said modulation involves activation of GSK-3β activity and said agent is selected from the group consisting of an adenosine A1 receptor agonist (A1RAg), an adenosine A3 receptor agonist (A3RAg), an adenosine A2 receptor **antagonist** (A2RAn) and a combination of the same.

3. The method of claim 1, wherein said modulation involves inhibition of GSK-3β activity and said agent is selected from the group consisting of an adenosine A1 receptor **antagonist** (A1RAn), an adenosine A3 receptor agonist (A3RAn), an adenosine A2 receptor agonist (A2RAg) and a combination of the same.

4. The method of claim 2, wherein said active agent is A1RAg.

5. The method of claim 5, wherein said A1RAg is selected from the group consisting of $N^{6\text{-cyclopenyl}}$ adenosine (CPA), 2-chloro-CPA (CCPA), $N^{6\text{-cyclohexyl}}$ adenosine (CHA), N6-(phenyl-2R-isopropyl)adenosine (R-PIA) and 8-{4-[{{[(2-aminoethyl)amino]carbonyl}methyl)oxyl-phenyl}-1,3-dipropylxanthine (XAC).

6. The method of claim 2, wherein said active agent is an adenosine A1 receptor agonist (A3RAg).

7. The method of claim 6, wherein said A3RAg is selected from the group consisting group consisting of 2-(4-aminophenyl)ethyladenosine (APNEA), N^6-(4-amino-3-iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and 1-deoxy-1-{6-[({3-iodophenyl} methyl)amino]-9H-purine-9-yl}-N-methyl-β-D-ribofuranuron-amide (IB-MECA) and 2-chloro-N^6-(2-iodobenzyl)-adenosine-5'-N-methly-uronamide (Cl-IB-MECA).

8. The method of claim 6, wherein the active agent is CI-IB-MECA.

9. The method of claim 6, wherein the active agent is a xanthine-7-riboside derivative.

10. The method of claim 2 wherein said active agent is an adenosine A2 receptor **antagonist** (A2RAn).

11. The method of claim 10, wherein said A2RAn is 3,7-dimethyl-1-propargyl-xantane (DMPX).

12. The method of claim 2, for the treatment of a disease or disorder which requires for its treatment elevation of GSK-3β activity.

13. The method of claim 12 wherein said disease is hair loss.

14. The method of claim 3, wherein said active agent is an A1RAn.

15. The method of claim 14, wherein said A1RAn is 1,3-dipropyl-8-cyclopentylxanthine (DPCPX).

16. The method of claim 3, wherein said active agent is an A3RAn.

17. The method of claim 16, wherein said A3RAn is selected from the group consisting of 5-propyl-2-ethyl-4-propyl-3-ethysulfanylcarbonyl)-6-phenylpyridine-5-carboxylate (MRS-1523) and 9-chloro-2-(2-furanyl)-5[(phenylacetyl)amino][1,2,4,]-triazolo[1,5-c]quinazoline (MRS-1200):

18. The method of claim 3, wherein said active agent is an adenosine A2RAg.

19. The method of claim 18, wherein said A2RAg is N^6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)-ethyl] adenosine (DMPA)

20. The method of claim 3, for the treatment of a disease or disorder which requires for its treatment suppression of GSK-3β activity.

21. The method of claim 20, wherein said disease is a disease associated with degeneration of cells.

22. The method of claim 20, wherein said disease is a neurodegenerative disease or a neurotraumatic disorder.

23. The method of claim 20, wherein said disorder is associated with psychiatric disorders.

24. The method of claim 20, wherein said disease is non-insulin dependent diabetes mellitus.

25. The method of claim 1, wherein said active agent is administered orally.

26. A pharmaceutical composition for achieving a therapeutic effect in a subject in need, the therapeutic effect comprising modulating GSK-3β activity in target cells, the composition comprising a therapeutically effective amount of an active agent and one or more pharmaceutically acceptable additives, said active agent is selected from the group consisting of an adenosine A1 receptor ligand (A1RL), an A2 **adenosine receptor** ligand (A2RL), an adenosine A3 receptor ligand and any combination of A1RL, A2RL and A3RL.

27. The composition of claim 26, wherein said modulation involves activation of GSK-3β activity and said agent is selected from the group consisting of an adenosine A1 receptor agonist (A1RAg), an

adenosine A3 receptor agonist (A3RAg), an adenosine A2 receptor **antagonist** (A2RAn) and a combination of the same.

28. The composition of claim 26, wherein said modulation is inhibition of GSK-3β activity and said agent is selected from the group consisting of an adenosine A1 receptor **antagonist** (A1RAn), an adenosine A3 receptor **antagonist** (A3RAn), an adenosine A2 receptor agonist (A2RAg) and a combination of the same.

29. The composition of claim 27, wherein said active agent is A1RAg.

30. The composition of claim 29, wherein said A1RAg is selected from the group consisting of the N6-cyclopentyl adenosine (CPA), 2-chloro-CPA (CCPA), N6-cyclohexyl adenosine (CHA), N6-phenyl-2R-isopropyl)adenosine (R-PIA) and 8-{4-[({[(2-aminoethyl)amino]carbonyl}methyl)oxyl-phenyl}-1,3-dipropylxanthine (XAC).

31. The composition of claim 27, wherein said active agent is an adenosine A3 receptor agonist (A3RAg).

32. The composition of claim 31, wherein said A3RAg is selected from the group consisting group consisting of 2-(4-aminophenyl)ethyladenosine (APNEA), N6-(4-amino-3- iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and 1-deoxy-1-{6- [({3-iodophenyl} methyl)amino]-9H-purine-9-yl}-N-methyl-β-D-ribofuranuron-amide (IB-MECA) and 2-chloro-N6-(2-iodobenzyl)-adenosine-5'-N-methly-uronamide (Cl-IB-MECA).

33. The composition of claim 32, wherein the active agent is Cl-IB-MECA.

34. The composition of claim 31, wherein the active agent is a xanthine-7-riboside derivative.

35. The composition of claim 27, wherein said active agent is an adenosine A2 receptor **antagonist** (A2RAn).

36. The composition of claim 35, wherein said A2RAn is 3,7-dimethyl-1-propargyl-xantane (DMPX).

37. The composition of claim 27, for the treatment of a disease or disorder which requires for its treatment elevation of GSK-3β activity.

38. The composition of claim 37, for the treatment of hair loss.

39. The composition of claim 28, wherein said active agent is an A3RAn.

40. The composition of claim 39, wherein said A3RAn is 5-propyl-2-ethyl-4propyl-3-ethylsulfanylcarbonyl)-6-phenylpyridine-5-carboxylate (MRS-1523) and 9-chloro-2-(2-furanyl)-5-[(phenylacetyl)amino][1,2,4,]-triazolo[1,5-c]quinazoline (MRS-1200).

41. The composition of claim 28, wherein said active agent is an A1RAn.

42. The composition of claim 41, wherein said A1RAn is 1,3-dipropyl-8-cyclopentylxanthine (DPCPX).

43. The composition of claim 28, wherein said active agent is an A2RAg.

44. The composition of claim 43, wherein said A2RAg is N6-[2-(3,5-dimethoxyphenyl)-2 -(methylphenyl)-ethyl]adenosine (DMPA).

45. The composition of claim 26, for the treatment of a disease or disorder which requires for its treatment suppression of GSK-3β activity.

46. The composition of claim 45, wherein said disease is a disease associated with degeneration of cells.

47. The composition of claim 45, wherein said disease is a neurodegenerative disease or a neurotraumatic disorder.

48. The composition of claim 45, wherein said disorder is associated

with psychiatric disorders.

49. The composition of claim 45, wherein said disease is non-insulin dependent diabetes mellitus.

50. The composition of claim 26, formulated for oral administration.

51. Use of an active agent selected from the group consisting of an adenosine A1 receptor ligand (A1RL), an adenosine A2 receptor ligand (A2RL), and an adenosine A3 receptor ligand (A3RL) and any combination of A1RL, A2RL and A3RL for modulating GSK-3β activity in cells.

52. Use according to claim 51, for elevating GSK-3β activity, wherein said active agent is selected from the group consisting of A1RAg, A3RAg, A2RAn and any combination of the same.

53. Use according to claim 51, for suppressing GSK-3β activity, wherein said active agent is selected from the group consisting of A1RAn, A3RAn, A2RAg and any combination of the same.

54. Use according to Claim 51, substantially as described in the specification.

L14 ANSWER 17 OF 56 USPATFULL on STN
2002:179184 Compounds specific to adenosine A3 receptor and uses thereof.
Castelhano, Arlindo L., New City, NY, UNITED STATES
McKibben, Bryan, White Plains, NY, UNITED STATES
Witter, David J., Putman Valley, NY, UNITED STATES
US 2002094974 A1 20020718
APPLICATION: US 2000-728616 A1 20001201 (9)
PRIORITY: US 1999-169036P 19991202 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A compound having the structure: ##STR257## wherein R_1 is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, or N-methylaminocarbonyl pyridyl-2- methyl; wherein R_3 and R_4 are independently H, substituted or unsubstituted alkyl, or aryl.

2. The compound of claim 1, having the structure: ##STR258##

3. The compound of claim 1, having the structure: ##STR259##

4. The compound of claim 1, having the structure: ##STR260##

5. The compound of claim 1, having the structure: ##STR261##

6. The compound of claim 1, having the structure: ##STR262##

7. The compound of claim 1, having the structure: ##STR263##

8. The compound of claim 7, having the structure: ##STR264##

9. The compound of claim 7, having the structure: ##STR265##

10. The compound of claim 7, having the structure: ##STR266##

11. The compound of claim 7, having the structure: ##STR267##

12. The compound of claim 1, having the structure: ##STR268##

13. The compound of claim 1, having the structure: ##STR269##

14. The compound of claim 1, having the structure: ##STR270##

15. The compound of claim 1, having the structure: ##STR271##

16. The compound of claim 1, having the structure: ##STR272##

17. The compound of claim 1, having the structure: ##STR273##

18. The compound of claim 17, having the structure: ##STR274##

19. The compound of claim 1, having the structure: ##STR275##

20. The compound of claim 19, having the structure: ##STR276##

21. The compound of claim 1, having the structure: ##STR277##

22. The compound of claim 21, having the structure: ##STR278##

23. The compound of claim 21, having the structure: ##STR279##

24. A compound having the structure: ##STR280## wherein R_1, R_2 and the nitrogen together are 3-hydroxy pyrrolidino, 3-methyloxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino, or 3-hydroxymethyl piperadino; wherein R_3 and R_4 are independently H, substituted or unsubstituted alkyl, or aryl.

25. The compound of claim 24, having the structure: ##STR281##

26. The compound of claim 25, having the structure: ##STR282##

27. The compound of claim 25, having the structure: ##STR283##

28. The compound of claim 24, having the structure: ##STR284##

29. The compound of claim 24, having the structure: ##STR285##

30. The compound of claim 29, having the structure: ##STR286##

31. The compound of claim 29, having the structure: ##STR287##

32. The compound of claim 24, having the structure: ##STR288##

33. The compound of claim 32, having the structure: ##STR289##

34. The compound of claim 32, having the structure: ##STR290##

35. The compound of claim 24, having the structure: ##STR291##

36. The compound of claim 35, having the structure: ##STR292##

37. The compound of claim 35, having the structure: ##STR293##

38. A compound having the structure: ##STR294##

39. A method for treating a disease associated with A_3 **adenosine receptor** in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claims 1, 24, or 38.

40. The method of claim 39, wherein the subject is a mammal.

41. The method of claim 40, wherein the mammal is a human.

42. The method of claim 39, wherein said A_3 **adenosine receptor** is associated with asthma, hypersensitivity, rhinitis, hay fever, serum sickness, allergic vasculitis, atopic dermantitis, dermantitis, psorasis, eczema, idiopathic pulmonary fibrosis, eosinophillic chlorecystitis, chronic airway inflammation, hypereosinophilic syndromes, eosinophilic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, carcinomatosis, eosinophilic granuloma, familial histiocytosis, hypertension, mast cell degranulation, tumor, cardiac hypoxia, cerebral ischemia, diuresis, renal failure, neurological disorder, mental disorder, cognitive disorder, myocardial ischemia, bronchoconstriction, arthritis, autoimmune disease, Crohn's disease, Grave's disease, diabetes, multiple sclerosis, anaemia, psoriasis, fertility disorders, lupus erthyematosus, reperfusion injury, brain arteriole diameter, the release of allergic mediators, scleroderma, stroke, global ischemia, central nervous system disorder, cardiovascular disorder, renal disorder, inflammatory disorder, gastrointestinal disorder, eye disorder, allergic disorder, respiratory disorder, or immunological

disorder.

43. A water-soluble prodrug of the compound of claims 1, 24, or 38, wherein said water-soluble prodrug that is metabolized in vivo to an active drug which selectively inhibit A_3 **adenosine receptor**.

44. The prodrug of claim 43, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis.

45. A pharmaceutical composition comprising the prodrug of claim 43 and a pharmaceutically acceptable carrier.

46. The pharmaceutical composition of claim 44, wherein said pharmaceutical composition is an ophthalmic formulation.

47. The pharmaceutical composition of claim 44, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

48. The pharmaceutical composition of claim 44, wherein said pharmaceutical composition is a systemic formulation.

49. A method for inhibiting the activity of an A_3 **adenosine receptor** in a cell, which comprises contacting said cell with a compound of claims 1, 24, or 38.

50. The method of claim 49, wherein the compound is an **antagonist** of said A_3 **adenosine receptor**.

51. A method for treating a gastrointestinal disorder in an subject, comprising administering to the an effective amount of the compound of claims 1, 24, or 38.

52. The method of claim 51, wherein said disorder is diarrhea.

53. The method of claim 51, wherein the subject is a human.

54. The method of claim 51, wherein the compound is an **antagonist** of A_3 **adenosine receptors**.

55. A method for treating respiratory disorder in a subject, comprising administering to the subject an effective amount of the compound of claims 1, 24, or 38.

56. The method of claim 55, wherein said disorder is asthma, chronic obstructive pulmonary disease, allergic rhinitis, or an upper respiratory disorder.

57. The method of claim 55, wherein the subject is a human.

58. The method of claim 55, wherein said compound is an **antagonist** of A_3 **adenosine receptors**.

59. A method for treating damage to the eye of a subject which comprises administering to said subject an effective amount of a compound of claims 1, 24, or 38.

60. The method of claim 59, wherein said damage comprises retinal or optic nerve head damage.

61. The method of claim 59, wherein said damage is acute or chronic.

62. The method of claim 59, wherein said damage is the result of glaucoma, edema, ischemia, hypoxia or trauma.

63. The method of claim 59, wherein the subject is a human.

64. The method of claim 59, wherein the compound is an **antagonist** of A_3 **adenosine receptors**.

65. A combination therapy for glycoma, comprising the compound of claims 1, 24, or 38, and a prostagladin agonist, β2-2 agonist, or a muniscrinic **antagonist**.

66. A pharmaceutical composition comprising a therapeutically effective

amount of the compound of claims 1, 24, or 38 and a pharmaceutically acceptable carrier.

67. The pharmaceutical composition of claim 66, wherein said therapeutically effective amount is effective to treat a respiratory disorder or a gastrointestinal disorder.

68. The pharmaceutical composition of claim 67, wherein said gastrointestinal disorder is diarrhea.

69. The pharmaceutical composition of claim 67, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

70. The pharmaceutical composition of claim 66, wherein said pharmaceutical composition is an ophthalmic formulation.

71. The pharmaceutical composition of claim 66, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

72. The pharmaceutical composition of claim 66, wherein said pharmaceutical composition is a systemic formulation.

73. The pharmaceutical composition of claim 66, wherein said pharmaceutical composition is a surgical irrigating solution.

74. A packaged pharmaceutical composition for treating a disease associated with A_3 **adenosine receptor** in a subject, comprising: (a) a container holding a therapeutically effective amount of the compound of claims 1, 24, or 38; and (b) instructions for using said compound for treating said disease in a subject.

75. A method of preparing the compound of claim 1, comprising the steps of ##STR295## wherein R_1 is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, or N-methylaminocarbonyl pyridyl-2-methyl; wherein R_3 and R_4 are independently H, substituted or unsubstituted alkyl, or aryl.

L14 ANSWER 18 OF 56 USPATFULL on STN
2002:156711 METHODS OF PREVENTING OR TREATING CARDIOVASCULAR, CEREBROVASCULAR AND THROMBOTIC DISORDERS WITH TUMOR NECROSIS FACTOR **ANTAGONISTS**.
ELLIOTT, MICHAEL J., LONDON, UNITED KINGDOM
MAINI, RAVINDER N., LONDON, UNITED KINGDOM
FELDMANN, MARC, LONDON, UNITED KINGDOM
US 2002081306 A1 20020627
APPLICATION: US 1996-602272 A1 19960216 (8)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for treating or preventing a cardiovascular disorder in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a tumor necrosis factor **antagonist**.

2. A method of claim 1 wherein the cardiovascular disorder is selected from the group consisting of: acute mycocardial infarction, deep vein thrombosis and thrombophlebitis.

3. A method of claim 2 wherein the cardiovascular disorder is acute mycocardial infarction.

4. A method for treating or preventing a cerebrovascular disorder in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a tumor necrosis factor **antagonist**.

5. A method of claim 4 wherein the cerebrovascular disorder is stroke.

6. A method of treating or preventing a thrombotic disorder in an individual in need thereof comprising administering a therapeutically

effective amount of a tumor necrosis factor **antagonist** to the individual.

7. A method of claim 6 wherein the thrombotic disorder is selected from the group consisting of: a thromboembolic disorder, a ischemic event, stroke, acute mycocardial infarction, deep vein thrombosis and thrombophlebitis.

8. A method of claim 7 wherein the tumor necrosis factor **antagonist** is an anti-tumor necrosis factor antibody or fragment thereof.

9. A method of claim 8 wherein the antibody is selected from the group consisting of: a chimeric antibody, a humanized antibody and a resurfaced antibody or fragment thereof.

10. A method of claim 9 wherein the antibody binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 59-80.

11. A method of claim 9 wherein the antibody binds to the epitope of A2.

12. A method of claim 9 wherein the antibody is a chimeric antibody.

13. A method of claim 12 wherein the antibody binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 59-80.

14. A method of claim 12 wherein the antibody binds to the epitope of cA2.

15. A method of claim 14 wherein the antibody is cA2.

16. A method of claim 7 wherein the tumor necrosis factor **antagonist** is a receptor molecule, derivative or a fragment thereof which binds to tumor necrosis factor.

17. A method of claim 16 wherein the receptor molecule is selected from the group consisting of: p55 tumor necrosis factor receptor and p75 tumor necrosis factor receptor or functional portions thereof.

18. A method of claim 16 wherein the receptor molecule is selected from the group consisting of: the extracellular domain of p55 tumor necrosis factor receptor and the extracellular domain of p75 tumor necrosis factor receptor.

19. A method of claim 16 wherein the receptor molecule is a TNF receptor multimeric molecule or a functional portion thereof.

20. A method of claim 19 wherein the tumor necrosis receptor multimeric molecule comprises all or a functional portion of two or more extracellular domains of tumor necrosis factor receptors linked via one or more polypeptide linkers.

21. A method of claim 16 wherein the receptor molecule is an immunoreceptor fusion molecule or functional portion thereof.

22. A method of claim 21 wherein the immunoreceptor fusion molecule comprises all or a functional portion of a tumor necrosis factor receptor and an immunoglobulin chain.

23. A method of claim 7 wherein the tumor necrosis factor **antagonist** prevents or inhibits tumor necrosis factor synthesis or tumor necrosis factor release.

24. A method of claim 23 wherein the tumor necrosis factor **antagonist** is a phosphodiesterase inhibitor.

25. A method of claim 24 wherein the phosphodiesterase inhibitor is selected from the group consisting of: pentoxifylline and rolipram.

26. A method of claim 23 wherein the tumor necrosis factor **antagonist** is selected from the group consisting of: thalidomide and tenidap.

27. A method of claim 23 wherein the tumor necrosis factor is selected from the group consisting of: a A2b **adenosine receptor** agonist and a

A2b **adenosine receptor** enhancer.

28. A method of claim 7 wherein the tumor necrosis factor **antagonist** prevents or inhibits tumor necrosis factor receptor signalling.

29. A method of decreasing plasma fibrinogen in an individual comprising administering a therapeutically effective amount of a tumor necrosis factor **antagonist** to the individual.

30. A method of claim 29 wherein the tumor necrosis factor **antagonist** is an anti-tumor necrosis factor antibody or fragment thereof.

31. A method of claim 30 wherein the antibody is selected from the group consisting of: a chimeric antibody, a humanized antibody and a resurfaced antibody or fragment thereof.

32. A method of claim 31 wherein the antibody binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 59-80.

33. A method of claim 32 wherein the antibody binds to the epitope of A2.

34. A method of claim 31 wherein the antibody is a chimeric antibody.

35. A method of claim 34 wherein the antibody binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 59-80.

36. A method of claim 34 wherein the antibody binds to the epitope of cA2.

37. A method of claim 36 wherein the antibody is cA2.

38. A method of claim 29 wherein the tumor necrosis factor **antagonist** is a receptor molecule, derivative or a fragment thereof which binds to tumor necrosis factor.

39. A method of claim 38 wherein the receptor molecule is selected from the group consisting of: p55 tumor necrosis factor receptor and p75 tumor necrosis factor receptor or functional portions thereof.

40. A method of claim 38 wherein the receptor molecule is selected from the group consisting of: the extracellular domain of p55 tumor necrosis factor receptor and the extracellular domain of p75 tumor necrosis factor receptor.

41. A method of claim 40 wherein the receptor molecule is a tumor necrosis factor receptor multimeric molecule..

42. A method of claim 41 wherein the tumor necrosis factor receptor multimeric molecule comprises all or a functional portion of two or more extracellular domains of tumor necrosis factor receptors linked via one or more polypeptide linkers.

43. A method of claim 40 wherein the receptor molecule is an immunoreceptor fusion molecule or functional portion thereof.

44. A method of claim 43 wherein the immunoreceptor fusion molecule comprises all or a functional portion of a tumor necrosis factor receptor and an immunoglobulin chain.

45. A method of claim 29 wherein the tumor necrosis factor **antagonist** prevents or inhibits tumor necrosis factor synthesis or tumor necrosis factor release.

46. A method of claim 45 wherein the tumor necrosis factor **antagonist** is a phosphodiesterase inhibitor.

47. A method of claim 46 wherein the phosphodiesterase inhibitor is selected from the group consisting of: pentoxifylline and rolipram.

48. A method of claim 45 wherein the tumor necrosis factor **antagonist** is selected from the group consisting of: thalidomide and tenidap.

49. A method of claim 45 wherein the tumor necrosis factor **antagonist** is selected from the group consisting of: a A2b **adenosine receptor** agonist and a A2b **adenosine receptor** enhancer.

50. A method of claim 29 wherein the tumor necrosis factor **antagonist** prevents or inhibits tumor necrosis factor receptor signalling.

L14 ANSWER 19 OF 56 USPATFULL on STN
2002:148613 G protein coupled receptor (GPCR) agonists and **antagonists** and methods of activating and inhibiting GPCR using the same.
Kuliopulos, Athan, Winchester, MA, UNITED STATES
Covic, Lidija, Boston, MA, UNITED STATES
US 2002076755 A1 20020620
APPLICATION: US 2001-841091 A1 20010423 (9)
PRIORITY: US 2000-198993P 20000421 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A chimeric polypeptide, said chimeric polypeptide comprising: a) a first domain comprising extracellular or intracellular portions of a G protein coupled receptor, and b) at least a second domain, attached to the first domain, wherein said second domain is naturally or non-naturally occurring hydrophobic moieties, wherein said first domain does not comprise a native extracellular ligand of said GPCR.

2. The chimeric polypeptide of claim 1, wherein said second or more domains are attached at either one end, at both ends, or at an internal position of said first domain.

3. The chimeric polypeptide of claim 1, wherein said hydrophobic moiety is selected from the group consisting of: a lipid, an acyl or an amino acid.

4. The chimeric polypeptide of claim 3, wherein said hydrophobic moiety is selected from the group consisting of: palmitate (C16), myristoyl (C12), capryl (C10), caproyl (C6), phospholipids, steroids, sphingosines, ceramides, octyl-glycine, 2-cyclohexylalanine, or benzolylphenylalanine, wherein said hydrophobic moiety is attached to said chimeric polypeptide with amide bonds, sulfhydryls, amines, alcohols, phenolic groups, or carbon-carbon bonds.

5. The chimeric polypeptide of claim 1, wherein said extracellular portion is selected from the group consisting of: the first extracellular domain or a fragment thereof, the second extracellular loop or a fragment thereof, the third extracellular loop or a fragment thereof, and the fourth extracellular loop or a fragment thereof, of said G-protein coupled receptor.

6. The chimeric polypeptide of claim 1, wherein said intracellular portion is selected from the group consisting of: the first intracellular loop or a fragment thereof, the second intracellular loop or a fragment thereof, the third intracellular loop or a fragment thereof, and the fourth intracellular domain or a fragment thereof, of said G-protein coupled receptor.

7. The chimeric polypeptide of claim 1 wherein said intracellular portion is selected from the group consisting of: an intracellular domain of a one-transmembrane domain G-protein coupled receptor of the cytokine GPCR, or a fragment thereof, or an intracellular domain of a multi-polypeptide-GPCR.

8. The chimeric polypeptide of claim 7, wherein said multi-polypeptide-GPCRs is selected from the group consisting of: a GPIb/V/IX receptor or a collagen receptor.

9. The chimeric polypeptide of claim 5, wherein said extracellular portion of the GPCR is at least 3 contiguous amino acid residues.

10. The chimeric polypeptide of claim 6, where said intracellular portion is at least 3 contiguous amino acid residues.

11. The chimeric polypeptide of claim 6, wherein said intracellular portion is at least 5 contiguous amino acid residues.

12. The chimeric polypeptide of claim 6, wherein said intracellular portion comprises the third intracellular loop of the GPCR.

13. The chimeric polypeptide of claim 12, wherein said intracellular portion comprises at least 7 contiguous amino acid residues of the third intracellular loop.

14. The chimeric polypeptide of claim 1, wherein said second domain comprises a GPCR transmembrane domain or a fragment thereof.

15. The chimeric polypeptide of claim 14, wherein said transmembrane domain comprises at least 7 amino acid residues of TM5.

16. The chimeric polypeptide of claim 15, wherein said transmembrane domain comprises at least 14 amino acid residues of TM5.

17. The chimeric polypeptide of any one of claims 14, 15, or 16, wherein said amino acid residues are contiguous amino acid residues of TM5.

18. The nucleic acid of claim 1, wherein said G-protein coupled receptor is a mammalian G-protein coupled receptor.

19. The chimeric polypeptide of claim 18, wherein the G-protein coupled receptor or fragment thereof, is selected from the group consisting of a luteinizing hormone receptor, a follicle stimulating hormone receptor, a thyroid stimulating hormone receptor, a calcitonin receptor, a glucagon receptor, a glucagon-like peptide 1 receptor (GLP-1), a metabotropic glutamate receptor, a parathyroid hormone receptor, a vasoactive intestinal peptide receptor, a secretin receptor, a growth hormone releasing factor (GRF) receptor, protease-activated receptors (PARs), cholecystokinin receptors, somatostatin receptors, melanocortin receptors, ADP receptors, **adenosine receptors**, thromboxane receptors, platelet activating factor receptor, adrenergic receptors, 5-HT receptors, CXCR4, CCR5, chemokine receptors, neuropeptide receptors, opioid receptors, erythropoietin receptor, von Willebrand receptor, parathyroid hormone (PTH) receptor, vasoactive intestinal peptide (VIP) receptor, and collagen receptors.

20. The chimeric polypeptide of claim 1, wherein the hydrophobic moiety is a lipid.

21. The chimeric polypeptide of claim 20, wherein said lipid is a palmitate lipid.

22. A nucleic acid encoding the polypeptide of claim 1.

23. A recombinant vector comprising a nucleic acid of claim 22.

24. A host cell transformed with the recombinant vector of claim 23.

25. A method for producing a polypeptide of claim 1, comprising cultivating the host cell of claim 22 under conditions sufficient to express the receptor.

26. A method for identifying a potential therapeutic agent for use in treatment of a pathology, wherein the pathology is related to aberrant expression or aberrant physiological interactions of a GPCR, the method comprising: (a) providing a cell having a GPCR or a property or function ascribable to said GPCR; (b) contacting the cell with a composition comprising a candidate substance; and (c) contacting the cell with a composition comprising the chimeric polypeptide of claim 1; and (d) determining whether the composition comprising the candidate substance alters the property or function ascribable to said GPCR; whereby, if an alteration observed in the presence of the substance is not observed when the cell is contacted with a composition devoid of the substance, the substance is identified as a potential therapeutic agent.

27. A method of treating or preventing a pathology associated with a GPCR, said method comprising administering the polypeptide of claim 1 to a subject in which such treatment or prevention is desired in an amount sufficient to treat or prevent said pathology in said subject.

28. The method of claim 27, wherein said subject is a human.

29. A pharmaceutical composition comprising the chimeric polypeptide of

claim 1 and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising the nucleic acid molecule of claim 22 and a pharmaceutically acceptable carrier.

31. A kit comprising in one or more containers, the pharmaceutical composition of claim 29.

32. The use of a therapeutic in the manufacture of a medicament for treating a syndrome associated with a human disease, the disease selected from a pathology associated with the polypeptide of claim 1, wherein said therapeutic is the polypeptide of claim 1.

33. A method for screening for a modulator of activity of a GPCR, said method comprising: a) administering a test compound to a first test animal, wherein said test animal expresses a desired GPCR; b) administering a polypeptide of claim 1 to a second test animal; c) measuring the activity of said test compound in said first test animal and said polypeptide in said second test animal; and c) comparing the activity of said polypeptide in said second test animal with the activity of said test compound in said first test animal with the activity of the desired GPCR in a control animal not administered said polypeptide, wherein a change in the activity of said polypeptide in said first test animal relative to both said second test animal and said control animal indicates the test compound is a modulator of, an agonist of or an **antagonist** of said GPCR.

34. A method of treating a pathological state in a mammal, the method comprising administering to the mammal a polypeptide of claim 1.

```
=> d his

     (FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

     FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
                E WILSON CONSTANCE N/IN
L1             3 S E4

     FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
                E WILSON C N/IN
L2            19 S E3
L3             8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
                E WILSON C N/AU
L4            96 S E3
L5             1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6          2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7          1803 S L6 AND ANTAGONIST?
L8           319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9           140 S L8 AND ANTAGONIST?/CLM
L10           61 S L9 AND AY<2002
L11            4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12           57 S L10 NOT L11
L13            1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14           56 S L10 NOT (L11 OR L13)

=> s l9 and (P2X receptor?/clm or P2? purinoceptor?/clm)
             56 P2X/CLM
          33486 RECEPTOR?/CLM
             15 P2X RECEPTOR?/CLM
                   ((P2X(W)RECEPTOR?)/CLM)
           5939 P2?/CLM
             39 PURINOCEPTOR?/CLM
              5 P2? PURINOCEPTOR?/CLM
                   ((P2?(W)PURINOCEPTOR?)/CLM)
L15           10 L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)

=> d l15,cbib,clm,1-10

L15  ANSWER 1 OF 10  USPATFULL on STN
```

2006:315846 Methanocarba cycloalkyl nucleoside analogues.
Jacobson, Kenneth A., Silver Spring, MD, UNITED STATES
Marquez, Victor E., Montgomery Village, MD, UNITED STATES
Govt of the U.S.A., represented by the Secretary, Dept of Health & Human Services, Rockville, MD, UNITED STATES, 20852 (U.S. corporation)
US 2006270629 A1 20061130
APPLICATION: US 2006-500860 A1 20060808 (11)
PRIORITY: US 2000-176373P 20000114 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A compound having the formula A-M, wherein A is a chemically modified adenine or uracil and M is a constrained cycloalkyl group, said adenine or uracil is bonded to said constrained cycloalkyl group, and said compound binds a receptor; or a salt of said compound.

2. The compound of claim 1, wherein said receptor is a P1 or P2 receptor.

3. The compound of claim 2, wherein said P1 receptor is selected from the group consisting of A_1, A_{2A}, and A_3.

4. The compound of claim 2, wherein said P2 receptor is selected from the group consisting of P2Y and P2X.

5. The compound of claim 1, wherein said constrained cycloalkyl group includes a cyclopentyl group.

6. The compound of claim 3, wherein said constrained cyclopentyl group is a cyclopentyl ring derivatized with a fused cyclopropane bridge.

7. The compound of claim 1, wherein said constrained cycloalkyl group is constrained in the N-conformation.

8. The compound of claim 1, wherein said constrained cycloalkyl group is constrained in the S-conformation.

9. A compound of the formula ##STR8## wherein R_1 is hydrogen, alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, arylalkyl, acyl, sulfonyl, arylsulfonyl, thiazolyl or bicyclic alkyl; R_2 is hydrogen, halo, alkyl, aryl, arylamino, aryloxide, alkynyl, alkenyl, thiol, cyano, or; R_3, R_4, and R_5, are each independently hydrogen, hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, aryl, acyl, alkylamino, arylamino, phosphoryl, diphosphoryl, triphosphoryl, phosphonyl, boronyl, thiophosphoryl, thiodiphosphoryl, thiotriphosphoryl or vanadyl, and can be the same or different; R_6 is hydrogen, alkyl, alkenyl, alkynyl, heteroaryl or aminoalkyl; R_7 is methylene, dihalomethyl, carbonyl, sulfoxide; and at least one of R_1, R_2, and R_6 is other than hydrogen; R_8 is carbon or nitrogen; or a salt of said compound.

10. The compound of claim 9, wherein R_1 is alkyl, cycloalkyl, alkoxy, aryl, arylalkyl, bicycloalkyl, or sulfonyl.

11. The compound of claim 9, wherein R_1 is methyl, cyclopentyl, cyclohexyl, phenyl, R-phenylisopropyl, benzyl, or phenylethyl; R_2 is chloro; and R_6 is C_{1-C6} alkylamino, C_{1-C6} alkyl, C_{2-C6} alkenyl, C_{2-C6} alkynyl.

12. The compound of claim 9, wherein R_1 is further substituted with a member selected from the group consisting of hydroxyl, halo, sulfonyl, amino, cyano, alkoxyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, sulfonamido, carboxyl, and carboxamido.

13. The compound of claim 9, wherein R_1 is methyl group and R_2 is chloro, alkylthio, or arylalkylthio.

14. The compound of claim 9, wherein R_6 is methyl and R_2 is chloro, alkylthio, arylalkylthio or hydrogen.

15. The compound of claim 9, wherein R_6 is halo and R_2 is a chloro, alkylthio, arylalkylthio or hydrogen.

16. The compound of claim 9, wherein R_2 is chloro.

17. The compound of claim 9, wherein R_1 is methyl and R_2 is chloro and R_3 is hydrogen.

18-20. (canceled)

21. A compound selected from the group consisting of: ##STR9## wherein R_1, R_2, R_9 is hydrogen, alkyl, alkenyl, alkynyl, aminoalkyl and R_3, R_4, and R_5, are each independently hydrogen, hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, aryl, acyl, alkylamino, arylamino, phosphoryl, phosphonyl, boronyl, or vanadyl, and can be the same or different; R_6 and R_7 are each independently sulfur or oxygen; and R_{10} is methylene, dihalomethyl, carbonyl, sulfoxide; or a salt of said compound.

22. The compound of claim 21, wherein R_1 is methyl.

23. A compound comprising a methanocarbocyclic analog of a chemically modified adenosine or uradine wherein said compound is a P2 receptor ligand; or a salt of said compound.

24. The compound of claim 23, wherein the compound is a P2 receptor agonist.

25. The compound of claim 23, wherein the compound is a P2 receptor **antagonist**.

26. The compound of claim 22, wherein said P2 receptor is selected from the group consisting of P2Y and P2X.

27. The compound of claim 22, wherein said P2 receptor is a P2Y receptor.

28. The compound of claim 22, wherein said P2 receptor is a P2Y1 receptor.

29. The compound of claim 22, wherein said P2 receptor is a **P2X receptor**.

30. A compound comprising a methanocarbocyclic analog of a chemically modified adenosine or uradine wherein said compound is a P1 receptor ligand; or a salt of said compound.

31. The compound of claim 30, wherein the compound is a P1 receptor agonist.

32. The compound of claim 30, wherein the compound is a P1 receptor **antagonist**.

33. The compound of claim 30, wherein said P1 receptor is selected from the group consisting of A_1, A_{2A}, and A_3.

34. The compound of claim 30, wherein said P1 receptor is A_1 receptor.

35. The compound of claim 30, wherein said P1 receptor is A_3 receptor.

36. A method of treating or preventing in a mammal a disease, state, or condition that responds to an adenosine, ATP, or UTP receptor agonist or **antagonist** comprising administering to the mammal a compound of claim 1.

37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 1.

38-39. (canceled)

40. A method for the treatment of airway diseases, cancer, cardiac arrhythmia, cardiac ischemia, epilepsy, Huntington's Disease, immunodeficient disorders, inflammatory disorders, neonatal hypoxia, neurodegenerative, pain, Parkinson's Disease, renal failure, schizophrenia, sleep disorders, stroke, thrombosis, urinary incontinence, diabetes, psoriasis, septic shock, brain trauma, glaucoma, or congestive heart failure in individuals in need of such treatment

comprising contacting an effective quantity of a compound of claim 1.

41. A method of treating or preventing in a mammal a disease, state, or condition that responds to an adenosine, ATP or UTP receptor agonist or **antagonist** comprising administering to the mammal a compound of claim 9.

42. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 9.

43. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 21.

44. A method of treating or preventing in a mammal a disease, state, or condition that responds to an adenosine, ATP, or UTP receptor agonist or **antagonist** comprising administering to the mammal a compound of claim 21.

45. A method for the treatment of airway diseases, cancer, cardiac arrhythmia, cardiac ischemia, epilepsy, Huntington's Disease, immunodeficient disorders, inflammatory disorders, neonatal hypoxia, neurodegenerative, pain, Parkinson's Disease, renal failure, schizophrenia, sleep disorders, stroke, thrombosis, urinary incontinence, diabetes, psoriasis, septic shock, brain trauma, glaucoma, or congestive heart failure in individuals in need of such treatment comprising contacting an effective quantity of a compound of claim 9.

46. A method for the treatment of airway diseases, cancer, cardiac arrhythmia, cardiac ischemia, epilepsy, Huntington's Disease, immunodeficient disorders, inflammatory disorders, neonatal hypoxia, neurodegenerative, pain, Parkinson's Disease, renal failure, schizophrenia, sleep disorders, stroke, thrombosis, urinary incontinence, diabetes, psoriasis, septic shock, brain trauma, glaucoma, or congestive heart failure in individuals in need of such treatment comprising contacting an effective quantity of a compound of claim 21.

L15 ANSWER 2 OF 10 USPATFULL on STN
2005:190059 Purine receptor inhibition as a therapeutic strategy in spinal cord and brain.
Nedergaard, Maiken, Webster, NY, UNITED STATES
Goldman, Steven A., Webster, NY, UNITED STATES
US 2005164975 A1 20050728
APPLICATION: US 2004-979526 A1 20041102 (10)
PRIORITY: US 2003-516677P 20031103 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating a subject with acute spinal cord injury, said method comprising: administering a purine receptor **antagonist** to the subject under conditions effective to treat spinal cord injury, wherein the purine receptor **antagonist** inhibits P2X purine receptor activation.

2. The method according to claim 1, wherein said administering is carried out orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by implantation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, transdermally, or by application to mucous membranes.

3. The method according to claim 1, wherein the purine receptor **antagonist** is administered with a pharmaceutically-acceptable carrier.

4. The method according to claim 1, wherein the subject is a human.

5. The method according to claim 1, wherein the purine receptor **antagonist** is a P2X7 purine receptor **antagonist**.

6. The method according to claim 5, wherein the P2X7 purine receptor **antagonist** is selected from the group consisting of 1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine, hexamethylene amiloride, oxidized ATP, and brilliant blue G.

7. A method of treating a subject with spinal cord ischemia resulting from stroke or vascular insult, interruption, or mechanical injury, said

method comprising: administering a purine receptor **antagonist** to the subject under conditions effective to treat spinal cord ischemia resulting from stroke or vascular insult, interruption, or mechanical injury, wherein the purine receptor **antagonist** inhibits P2X purine receptor activation.

8. The method according to claim 7, wherein said administering is carried out orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by implantation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, transdermally, or by application to mucous membranes.

9. The method according to claim 7, wherein the purine receptor **antagonist** is administered with a pharmaceutically-acceptable carrier.

10. The method according to claim 7, wherein the subject is a human.

11. The method according to claim 7, wherein the purine receptor **antagonist** is a P2X7 purine receptor **antagonist**.

12. The method according to claim 11, wherein the P2X7 purine receptor **antagonist** is selected from the group consisting of 1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine, hexamethylene amiloride, oxidized ATP, and brilliant blue G.

13. The method according to claim 7, wherein the mechanical injury is due to extradural cord compression, spinal cord trauma, or spinal cord surgery.

14. A method of treating a subject with ischemic or traumatic insults of brain tissue in regions expressing **P2X receptors**, said method comprising: administering a purine receptor **antagonist** to the subject under conditions effective to treat ischemic or traumatic insults of brain tissue in regions expressing **P2X receptors**, wherein the purine receptor **antagonist** inhibits P2X purine receptor activation.

15. The method according to claim 14, wherein said administering is carried out orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by implantation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, transdermally, or by application to mucous membranes.

16. The method according to claim 14, wherein the purine receptor **antagonist** is administered with a pharmaceutically-acceptable carrier.

17. The method according to claim 14, wherein the subject is a human.

18. The method according to claim 14, where the purine receptor **antagonist** is a P2X7 purine receptor **antagonist**.

19. The method according to claim 18, wherein the P2X7 purine receptor **antagonist** is selected from the group consisting of 1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine, hexamethylene amiloride, oxidized ATP, and brilliant blue G.

20. A method of inhibiting ATP-triggered brain or spinal cord cell death, said method comprising: contacting brain or spinal cord cells with a purine receptor **antagonist** under conditions effective to inhibit ATP-triggered brain or spinal cord cell death, wherein the purine receptor **antagonist** inhibits P2X purine receptor activation.

21. The method according to claim 20, wherein the brain or spinal cord cells are neural cells.

22. The method according to claim 21, wherein the neural cells are astrocytes.

23. The method according to claim 21, wherein the neural cells are neurons.

24. The method according to claim 21, wherein the neural cells are

oligodendrocytes.

25. The method according to claim 20, wherein the brain or spinal cord cells are endothelial cells.

26. The method according to claim 20, wherein the method inhibits ATP-triggered brain cell death.

27. The method according to claim 26, wherein the brain cell death results from vascular insufficiency.

28. The method according to claim 26, wherein the brain cell death results from stroke.

29. The method according to claim 26, wherein the brain cell death results from traumatic brain injury.

30. The method according to claim 20, wherein the method inhibits ATP-triggered spinal cord cell death.

31. The method according to claim 20, wherein the brain or spinal cord cells are human brain or spinal cord cells.

32. The method according to claim 20, where the purine receptor **antagonist** is a P2X7 purine receptor **antagonist**.

33. The method according to claim 32, wherein the P2X7 purine receptor **antagonist** is selected from the group consisting of 1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine, hexamethylene amiloride, oxidized ATP, and brilliant blue G.

L15 ANSWER 3 OF 10 USPATFULL on STN
2005:183939 Methods of modulating smooth muscle contractility.
Chen, Zunxuan, King of Prussia, PA, UNITED STATES
Hu, Erding, King of Prussia, PA, UNITED STATES
Westfall, Timothy D., King of Prussia, PA, UNITED STATES
Wibberley, Alexandria, King of Prussia, PA, UNITED STATES
US 2005159333 A1 20050721
APPLICATION: US 2003-513139 A1 20030430 (10)
WO 2003-US13385 20030430
PRIORITY: US 2002-60377504 20020502
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method for modulating bladder smooth muscle activity comprising the step of contacting a polypeptide in a ROCK pathway with a compound that modulates an activity of said polypeptide.

2. The method of claim 1 wherein said polypeptide is ROCK 1 or ROCK 2 or both.

3. The method of claim 1 wherein said activity of said polypeptide is selected from the group consisting of: a response to carbachol, a response to neurokinin A, a response to a **P2X receptor antagonist**, and a response to electrical stimulus.

4. The method of claim 3 wherein said response is bladder contraction.

5. The method of claim 1 wherein said bladder smooth muscle activity is contractility.

6. A method of treating a mammal for a lower urinary tract disorder or overactive bladder comprising the step of modulating bladder smooth muscle activity.

7. A method of treating a mammal for a lower urinary tract disorder or overactive bladder comprising contacting said mammal with a compound that modulates an activity of a polypeptide in a ROCK pathway.

8. The method of claim 7 wherein said polypeptide is ROCK 1 or ROCK 2 or both.

9. The method of claim 7 wherein said activity of said polypeptide is

selected from the group consisting of: a response to carbachol, a response to neurokinin A, a response to a **P2X receptor antagonist**, and a response to electrical stimulus.

10. The method of claim 9 wherein said response is bladder contraction.

11. The method of claim 6 wherein said bladder smooth muscle activity is contractility.

12. The method of claim 6 wherein said bladder smooth muscle activity is related to expression or activity of ROCK 1 or ROCK 2 or both.

13. The method of claim 12 wherein said activity of ROCK I or ROCK 2 or both is selected from the group consisting of: a response to carbachol, a response to neurokinin A, a response to a **P2X receptor antagonist**, and a response to electrical stimulus.

14. The method of claim 13 wherein said response is bladder contraction.

15. The method of claim 14 wherein said bladder smooth muscle activity is contractility.

L15 ANSWER 4 OF 10 USPATFULL on STN
2005:176850 Parakeratosis inhibitor, pore-shrinking agent and skin preparation for external use.
Katsuta, Yuji, Yokohama-shi, JAPAN
Inomata, Shinji, Yokohama-shi, JAPAN
Shiseido Co., Ltd. (non-U.S. corporation)
US 2005152930 A1 20050714
APPLICATION: US 2003-515219 A1, 20030523 (10)
WO 2003-JP6467 20030523
PRIORITY: JP 2002-153457 20020528
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A parakeratosis inhibitor comprising an **antagonist** to an excitatory cell receptor or an agonist to an inhibitory cell receptor.

2. The parakeratosis inhibitor according to claim 1, wherein the excitatory cell receptor is a glutamic acid receptor or an ATP receptor.

3. The parakeratosis inhibitor according to claim 2, wherein the glutamic acid receptor is an N-methyl-D-aspartic acid receptor.

4. The parakeratosis inhibitor according to claim 3, wherein the **antagonist** to the N-methyl-D-aspartic acid receptor is dizocylpin or D-glutamic acid.

5. The parakeratosis inhibitor according to claim 2, wherein the ATP receptor is a **P2X receptor**.

6. The parakeratosis inhibitor according to claim 5, wherein the **antagonist** to the ATP receptor is suramin, pyridoxal phosphate-6-azophenyl-2',4'-disulfonic acid or trinitrophenyl-ATP.

7. The parakeratosis inhibitor according to claim 1, wherein the inhibitory cell receptor is a γ-aminobutyric acid receptor or a glycine receptor.

8. The parakeratosis inhibitor according to claim 7, wherein the γ-aminobutyric acid receptor is a Cl-- channel-involving bicuculline sensitive receptor.

9. The parakeratosis inhibitor according to claim 8, wherein the agonist to the Cl-- channel-involving bicuculline sensitive receptor is γ-aminobutyric acid, muscimol or isogubacin.

10. The parakeratosis inhibitor according to claim 7, wherein the agonist to the glycine receptor is glycine.

11. A parakeratosis inhibitory skin preparation for external use comprising an **antagonist** to an excitatory cell receptor or an agonist to an inhibitory cell receptor.

12-16. (canceled)

17. The parakeratosis inhibitory skin preparation for external use according to claim 11, wherein the excitatory cell receptor is a glutamic acid receptor or an ATP receptor.

18. The parakeratosis inhibitory skin preparation for external use according to claim 11, wherein the **antagonist** to the excitatory cell receptor is dizocylpin, D-glutamic acid, suramin, pyridoxal phosphate-6-azophenyl-2',4'-disulfonic acid or trinitrophenyl-ATP.

19. The parakeratosis inhibitory skin preparation for external use according to claim 11, wherein the inhibitory cell receptor is a γ-aminobutyric acid receptor or a glycine receptor.

20. The parakeratosis inhibitory skin preparation for external use according to claim 11, wherein the agonist to the inhibitory cell receptor is a γ-aminobutyric acid, muscimol, isogubacin or glycine.

21. A pore-shrinking preparation comprising an **antagonist** to an excitatory cell receptor or an agonist to an inhibitory cell receptor.

22. The pore-shrinking preparation according to claim 21, wherein the excitatory cell receptor is a glutamic acid receptor or an ATP receptor.

23. The pore-shrinking preparation according to claim 22, wherein the glutamic acid receptor is an N-methyl-D-aspartic acid receptor.

24. The pore-shrinking preparation according to claim 23, wherein the **antagonist** to the N-methyl-D-aspartic acid receptor is dizocylpin or D-glutamic acid.

25. The pore-shrinking preparation according to claim 22, wherein the ATP receptor is a **P2X receptor**.

26. The pore-shrinking preparation according to claim 25, wherein the **antagonist** to the ATP receptor is suramin, pyridoxal phosphate-6-azophenyl-2',4'-disulfonic acid or trinitrophenyl-ATP.

27. The pore-shrinking preparation according to claim 21, wherein the inhibitory cell receptor is a γ-aminobutyric acid receptor or a glycine receptor.

28. The pore-shrinking preparation according to claim 27, wherein the γ-aminobutyric acid receptor is a Cl-- channel-involving bicuculline sensitive receptor.

29. The pore-shrinking preparation according to claim 28, wherein the agonist to the Cl-- channel-involving bicuculline sensitive receptor is γ-aminobutyric acid, muscimol or isogubacin.

30. The pore-shrinking preparation according to claim 27, wherein the agonist to the glycine receptor is glycine.

31. The pore-shrinking skin preparation for external use comprising an **antagonist** to an excitatory cell receptor or an agonist to an inhibitory cell receptor.

32. The pore-shrinking skin preparation for external use according to claim 31, wherein the excitatory cell receptor is a glutamic acid receptor or an ATP receptor.

33. The pore-shrinking skin preparation for external use according to claim 31, wherein the **antagonist** to the excitatory cell receptor is dizocylpin, D-glutamic acid, suramin, pyridoxal phosphate-6-azophenyl-2',4'-disulfonic acid or trinitrophenyl-ATP.

34. The pore-shrinking skin preparation for external use according to claim 31, wherein the inhibitory cell receptor is a γ-aminobutyric acid receptor or a glycine receptor.

35. The pore-shrinking skin preparation for external use according to claim 31, wherein the agonist to the inhibitory cell receptor is γ-aminobutyric acid, muscimol, isogubacin or glycine.

L15 ANSWER 5 OF 10 USPATFULL on STN
2005:87357 Screening method of drug for treatment of neuropathic pain.
Inoue, Kazuhide, Tokyo-To, JAPAN
Tsuda, Makoto, Tokyo-To, JAPAN
Koizumi, Schuichi, Tokyo-To, JAPAN
Kohsaka, Shinichi, Tokyo-To, JAPAN
JAPAN HEALTH SCIENCES FOUNDATION (non-U.S. corporation)
US 2005074819 A1 20050407
APPLICATION: US 2003-676289 A1 20031001 (10)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of identifying a compound useful for the treatment or prevention of tactile allodynia induced after nerve injury, comprising: (a) contacting a cell expressing $P2X_4$ receptor on the surface thereof, with a test compound, in the presence of $P2X_4$ receptor agonist, (b) determining whether or not said test compound inhibits an interaction of said $P2X_4$ receptor agonist and $P2X_4$ receptor on the surface of the cell, and (c) identifying the test compound which inhibits said interaction, as useful for the treatment or prevention of tactile allodynia induced after nerve injury.

2. (Cancel)

3. The method according to claim 1, wherein the cell is mammalian cell.

4. The method according to claim 1, wherein the cell does not express any **P2X receptors** other than $P2X_4$ receptor.

5. The method according to claim 1, wherein the $P2X_4$ receptor agonist is ATP or ADP.

6. The method according to claim 1, wherein the contacting step (a) comprises incubating the cell and the test compound in the absence of the $P2X_4$ receptor agonist, and then incubating them in the presence of the $P2X_4$ receptor agonist.

7. The method according to claim 1, wherein the determining step (b) comprises measuring $P2X_4$ receptor-mediated ion flux of at least one ion selected from the group consisting of Na+, K+, and Ca^{2+}.

8. The method according to claim 7, wherein the contacting step (a) is carried out in the presence of the ion.

9. The method according to claim 1, wherein the determining step (b) comprises comparing intensity of the interaction with that of control sample obtained in the absence of any test compounds.

10. A method of identifying a compound useful for the treatment or prevention of neuropathic pain, comprising: (a) contacting a microglia in inactive-form with a test compound, in the presence of microglia-activator, (b) determining whether or not said test compound inhibits an activation of said microglia, and (c) identifying the test compound which inhibits said activation, as useful for the treatment or prevention of neuropathic pain.

11. The method according to claim 10, wherein the neuropathic pain is tactile allodynia induced after nerve injury.

12. The method according to claim 10, wherein the microglia-activator is ATP or ADP.

13. The method according to claim 10, wherein the contacting step (a) comprises incubating the cell and the test compound in the absence of the microglia-activator, and then incubating them in the presence of the microglia-activator.

14. A pharmaceutical composition comprising a $P2X_4$ receptor inhibitor and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition according to claim 14 for use in

treatment or prevention of neuropathic pain.

16. The pharmaceutical composition according to claim 15, wherein the neuropathic pain is tactile allodynia induced after nerve injury.

17. The pharmaceutical composition according to claim 14, wherein the $P2X_4$ receptor inhibitor is a $P2X_4$ receptor **antagonist**.

18. The pharmaceutical composition according to claim 14, wherein the $P2X_4$ receptor inhibitor is an antibody or an antibody fragment which binds to $P2X_4$ receptor protein on the cell surface and prevents the interaction between the receptor and its agonist.

19. The pharmaceutical composition according to claim 14, wherein the $P2X_4$ receptor inhibitor is an antisense nucleic acid molecule that specifically suppresses expression of $P2X_4$ receptor gene.

20. The pharmaceutical composition according to claim 14, wherein the $P2X_4$ receptor inhibitor is an siRNA nucleic acid molecule that specifically suppresses expression of $P2X_4$ receptor gene.

21. The pharmaceutical composition according to claim 14, wherein the $P2X_4$ receptor inhibitor is a vector expressing an siRNA nucleic acid molecule that specifically suppresses expression of $P2X_4$ receptor gene.

22. A pharmaceutical composition comprising a microglial activation-inhibitor and a pharmaceutically acceptable carrier.

23. The pharmaceutical composition according to claim 22 for use in treatment or prevention of neuropathic pain.

24. The pharmaceutical composition according to claim 23, wherein the neuropathic pain is tactile allodynia induced after nerve injury.

25. The pharmaceutical composition according to claim 22, wherein the microglial activation-inhibitor is a $P2Y_{12}$ receptor inhibitor.

26. A method for treating or preventing neuropathic pain comprising administering to a subject a therapeutically effective amount of $P2X_4$ receptor inhibitor.

27. The method according to claim 26, wherein the neuropathic pain is tactile allodynia induced after nerve injury.

28. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is a $P2X_4$ receptor **antagonist**.

29. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is an antibody or an antibody fragment which binds to $P2X_4$ receptor protein on the cell surface and prevents the interaction between the receptor and its agonist.

30. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is an antisense nucleic acid molecule that specifically suppresses expression of $P2X_4$ receptor gene.

31. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is an siRNA nucleic acid molecule that specifically suppresses expression of $P2X_4$ receptor gene.

32. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is a vector expressing an siRNA nucleic acid molecule that specifically suppresses expression of $P2X_4$ receptor gene.

33. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is administered intraspinally.

34. The method according to claim 33, wherein the $P2X_4$ receptor inhibitor is administered by intrathecal injection.

35. The method according to claim 26, wherein the $P2X_4$ receptor inhibitor is administered in admixture with a pharmaceutically acceptable carrier.

36. A method for treating or preventing neuropathic pain comprising administering to a subject a therapeutically effective amount of microglial activation-inhibitor.

37. The method according to claim 36, wherein the neuropathic pain is tactile allodynia induced after nerve injury. 5.

38. The method according to claim 36, wherein the microglial activation-inhibitor is a $P2Y_{12}$ receptor inhibitor.

39. The method according to claim 36, wherein the microglial activation-inhibitor is administered intraspinally.

40. The method according to claim 39, wherein the microglial activation-inhibitor is administered by intrathecal injection.

41. The method according to claim 36, wherein the microglial activation-inhibitor is administered in admixture with a pharmaceutically acceptable carrier.

L15 ANSWER 6 OF 10 USPATFULL on STN
2003:306976 Methanocarba cycloakyl nucleoside analogues.
Jacobson, kenneth A, Silver Spring, MD, UNITED STATES
Marquez, Victor E, Montgomery, MD, UNITED STATES
US 2003216412 A1 20031120
APPLICATION: US 2002-169975 A1 20020712 (10)
WO 2001-US981 20010112
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A compound having the formula A-M, wherein A is a chemically modified adenine or uracil and M is a constrained cycloalkyl group, said adenine or uracil is bonded to said constrained cycloalkyl group, and said compound binds a receptor; or a salt of said compound.

2. The compound of claim 1, wherein said receptor is a P1 or P2 receptor.

3. The compound of claim 2, wherein said P1 receptor is selected from the group consisting of A_1,A_{2A}, and A_3.

4. The compound of claim 2, wherein said P2 receptor is selected from the group consisting of P2Y and P2X.

5. The compound of claim 1, wherein said constrained cycloalkyl group includes a cyclopentyl group.

6. The compound of claim 3, wherein said constrained cyclopentyl group is a cyclopentyl ring derivatized with a fused cyclopropane bridge.

7. The compound of claim 1, wherein said constrained cycloalkyl group is constrained in the N-conformation.

8. The compound of claim 1, wherein said constrained cycloalkyl group is constrained in the S-conformation.

9. A compound selected from the group consisting of ##STR15## wherein R_1 is hydrogen, alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, arylalkyl, acyl, sulfonyl, arylsulfonyl, thiazolyl or bicyclic alkyl; R_2 is hydrogen, halo, alkyl, aryl, arylamino, aryloxide, alkynyl, alkenyl, thiol, cyano, or; R_3, R_4, and R_5, are each independently hydrogen, hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, aryl, acyl, alkylamino, arylamino, phosphoryl, diphosphoryl, triphosphoryl, phosphonyl, boronyl, thiophosphoryl, thiodiphosphoryl, thiotriphosphoryl or vanadyl, and can be the same or different; R_6 is hydrogen, alkyl, alkenyl, alkynyl, heteroaryl or aminoalkyl; R_7 is methylene, dihalomethyl, carbonyl, sulfoxide; and at least one of R_1, R_2, and R_6 is other than hydrogen; R_8 is carbon or nitrogen; or a salt of said compound.

10. The compound of claim 9, wherein R_1 is alkyl, cycloalkyl, alkoxy, aryl, arylalkyl, bicycloalkyl, or sulfonyl.

11. The compound of claim 9, wherein R_1 is methyl, cyclopentyl, cyclohexyl, phenyl, R-phenylisopropyl, benzyl, or phenylethyl; R_2 is chloro; and R_6 is C_{1-C6} alkylamino, C_{1-C6} alkyl, C_{2-C6} alkenyl, C_{2-C6} alkynyl.

12. The compound of claim 9 or 10, wherein R_1 is further substituted with a member selected from the group consisting of hydroxyl, halo, sulfonyl, amino, cyano, alkoxyl, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, sulfonamido, carboxyl, and carboxamido.

13. The compound of claim 9, wherein R_1 is methyl group and R_2 is chloro, alkyithio, or arylalkylthio.

14. The compound of claim 9, wherein R_6 is methyl and R_2 is chloro, alkylthio, arylalkylthio or hydrogen.

15. The compound of claim 9, wherein R_6 is halo and R_2 is a chloro, alkylthio, arylalkylthio or hydrogen.

16. The compound of claim 9, wherein R_2 is chloro.

17. The compound of claim 9, wherein R_1 is methyl and R_2 is chloro and R_3 is hydrogen.

18. The compound of claim 9, wherein the compound has the formula ##STR16## wherein R_1 is iodobenzyl, or cyclopentyl and R_2 is hydrogen or chloro.

19. The compound of claim 9, wherein the compound has the formula ##STR17##

20. The compound of claim 9, wherein the compound has the formula ##STR18##

21. A compound selected from the group consisting of: ##STR19## wherein R_1, R_2, R_9 is hydrogen, alkyl, alkenyl, alkynyl, aminoalkyl and R_3, R_4, and R_5, are each independently hydrogen, hydroxyl, alkoxy, alkyl, alkenyl, alkynyl, aryl, acyl, alkylamino, arylamino, phosphoryl, phosphonyl, boronyl, or vanadyl, and can be the same or different; R_6 and R_7 are each independently sulfur or oxygen; and R_{10} is methylene, dihalomethyl, carbonyl, sulfoxide; or a salt of said compound.

22. The compound of claim 21, wherein R_1 is methyl.

23. A compound comprising a methanocarbocyclic analog of a chemically modified adenosine or uradine wherein said compound is a P2 receptor ligand; or a salt of said compound.

24. The compound of claim 23, wherein the compound is a P2 receptor agonist.

25. The compound of claim 23, wherein the compound is a P2 receptor **antagonist**.

26. The compound of claim 22, wherein said P2 receptor is selected from the group consisting of P2Y and P2X.

27. The compound of claim 22, wherein said P2 receptor is a P2Y receptor.

28. The compound of claim 22, wherein said P2 receptor is a P2Y1 receptor.

29. The compound of claim 22, wherein said P2 receptor is a **P2X receptor**.

30. A compound comprising a methanocarbocyclic analog of a chemically modified adenosine or uradine wherein said compound is a P1 receptor ligand; or a salt of said compound.

31. The compound of claim 30, wherein the compound is a P1 receptor

agonist.

32. The compound of claim 30, wherein the compound is a P1 receptor **antagonist**.

33. The compound of claim 30, wherein said P1 receptor is selected from the group consisting of A_1,A_{2A}, and A_3.

34. The compound of claim 30, wherein said P1 receptor is A_1 receptor.

35. The compound of claim 30, wherein said P1 receptor is A_3 receptor.

36. A method of treating or preventing in a mammal a disease, state, or condition that responds to an adenosine, ATP, or UTP receptor agonist or **antagonist** comprising administering to the mammal a compound of any of any of claims 1-36.

37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 1-36.

33. The use of a compound of any of claims 1-36 as a medicament.

34. The use of a methanocarba analog in the manufacture of a medicament for the treatment or prevention in a mammal a disease state, or condition that responds to an adenosine, ATP, UTP receptor agonist or **antagonist**.

35. A method for the treatment of airway diseases, cancer, cardiac arrhythmia, cardiac ischemia, epilepsy, Huntington's Disease, immunodeficient disorders, inflammatory disorders, neonatal hypoxia, neurodegenerative, pain, Parkinson's Disease, renal failure, schizophrenia, sleep disorders, stroke, thrombosis, urinary incontinence, diabetes, psoriasis, septic shock, brain trauma, glaucoma, or congestive heart failure in individuals in need of such treatment comprising contacting an effective quantity of a compound of any of claims 1-36.

L15 ANSWER 7 OF 10 USPATFULL on STN
2003:196062 Use of purinergic receptor modulators and related reagents.
Cockayne, Debra Ann, San Jose, CA, UNITED STATES
Ford, Anthony P.D.W., Mountain View, CA, UNITED STATES
Zhu, Quan-Ming, Sunnyvale, CA, UNITED STATES
Lachnit, Wilhelm G., Burlingame, CA, UNITED STATES
Malmberg, Annika B., Palo Alto, CA, UNITED STATES
US 2003135874 A1 20030717
APPLICATION: US 2002-304157 A1 20021126 (10)
PRIORITY: US 2000-182445P 20000215 (60)
US 2000-205798P 20000517 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating a subject having a disease state associated with a genitourinary or pain disorder comprising administering to the animal an effective amount of a purinoreceptor modulator.

2. The method of claim 1, wherein the genitourinary disorder is an overactive bladder.

3. The method of claim 1, wherein the genitourinary disorder is outlet obstruction.

4. The method of claim 1, wherein the genitourinary disorder is outlet insufficiency.

5. The method of claim 1, wherein the genitourinary disorder is pelvic hypersensitivity.

6. The method of claim 1, wherein the pain disorder is peripheral pain, inflammatory pain, or tissue injury pain.

7. The method of claim 1, wherein the purinoreceptor modulator is a **P2X receptor** complex modulator.

8. The method of claim 7, wherein the **P2X receptor** complex comprises at least one $P2X_3$ receptor subunit.

9. The method of claim 7, wherein the **P2X receptor** complex modulator is an **antagonist**.

10. The method of claim 7, wherein the **P2X receptor** complex modulator is an agonist.

11. The method of claim 1, wherein the subject is a mammal.

12. The method of claim 11, wherein the mammal is a human.

13. A transgenic animal containing an altered allele for the gene that naturally encodes and expresses a functional $P2X_3$ receptor subunit.

14. The transgenic animal of claim 13, wherein the altered allele is a non-functional allele.

15. The transgenic animal of claim 13, wherein the transgenic animal is a knockout (KO) animal.

16. The KO animal of claim 15, wherein the phenotype of the KO animal relative to a wild-type control animal comprises: a) an increase in urinary bladder capacity; b) a lower frequency of urine voiding; c) a larger voided volume; and d) no significant change in cystometric pressure.

17. The KO animal of claim 15, wherein the phenotype of the KO animal relative to a wild-type control animal comprises: a) attenuated nociception in response to injection of ATP; or b) attenuated nociception in response to injection of formalin.

18. The KO animal of claim 15, wherein the animal is a mouse.

19. A method for selecting a potential therapeutic compound for use in the treatment of a disease state associated with a genitourinary disorder comprising: a) administering the compound to a wild-type animal or an animal having a disease state associated with a genitourinary disorder; b) measuring the resulting phenotype of wild-type animal or the animal having the disease state; and c) comparing the resulting pheontype of the wild-type animal or the animal having the disease state to the phenotype of the knockout animal of claim 16.

20. A method for selecting a potential therapeutic compound for use in the treatment of a disease state associated with a pain disorder comprising: d) administering the compound to a wild-type animal or an animal having a disease state associated with a pain disorder; e) measuring the resulting phenotype of wild-type animal or the animal having the disease state; and f) comparing the resulting pheontype of the wild-type animal or the animal having the disease state to the phenotype of the knockout animal of claim 17.

L15 ANSWER 8 OF 10 USPATFULL on STN
2002:295072 Use of purinergic receptor modulators and related reagents.
Cockayne, Debra Ann, San Jose, CA, UNITED STATES
Ford, Anthony P.D.W., Mountain View, CA, UNITED STATES
Zhu, Quan-Ming, Sunnyvale, CA, UNITED STATES
Lachnit, Wilhelm G., Burlingame, CA, UNITED STATES
Malmberg, Annika B., Palo Alto, CA, UNITED STATES
US 2002165117 A1 20021107
APPLICATION: US 2001-783067 A1 20010213 (9)
PRIORITY: US 2000-182445P 20000215 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating a subject having a disease state associated with a genitourinary or pain disorder comprising administering to the animal an effective amount of a purinoreceptor modulator.

2. The method of claim 1, wherein the genitourinary disorder is an overactive bladder.

3. The method of claim 1, wherein the genitourinary disorder is outlet obstruction.

4. The method of claim 1, wherein the genitourinary disorder is outlet insufficiency.

5. The method of claim 1, wherein the genitourinary disorder is pelvic hypersensitivity.

6. The method of claim 1, wherein the pain disorder is peripheral pain, inflammatory pain, or tissue injury pain.

7. The method of claim 1, wherein the purinoreceptor modulator is a **P2X receptor** complex modulator.

8. The method of claim 7, wherein the **P2X receptor** complex comprises at least one $P2X_3$ receptor subunit.

9. The method of claim 7, wherein the **P2X receptor** complex modulator is an **antagonist**.

10. The method of claim 7, wherein the **P2X receptor** complex modulator is an agonist.

11. The method of claim 1, wherein the subject is a mammal.

12. The method of claim 11, wherein the mammal is a human.

13. A transgenic animal containing an altered allele for the gene that naturally encodes and expresses a functional $P2X_3$ receptor subunit.

14. The transgenic animal of claim 13, wherein the altered allele is a non-functional allele.

15. The transgenic animal of claim 13, wherein the transgenic animal is a knockout (KO) animal.

16. The KO animal of claim 15, wherein the phenotype of the KO animal relative to a wild-type control animal comprises: a) an increase in urinary bladder capacity; b) a lower frequency of urine voiding; c) a larger voided volume; and d) no significant change in cystometric pressure.

17. The KO animal of claim 15, wherein the phenotype of the KO animal relative to a wild-type control animal comprises: a) attenuated nociception in response to injection of ATP; or b) attenuated nociception in response to injection of formalin.

18. The KO animal of claim 15, wherein the animal is a mouse.

19. A method for selecting a potential therapeutic compound for use in the treatment of a disease state associated with a genitourinary disorder comprising: a) administering the compound to a wild-type animal or an animal having a disease state associated with a genitourinary disorder; b) measuring the resulting phenotype of wild-type animal or the animal having the disease state; and c) comparing the resulting pheontype of the wild-type animal or the animal having the disease state to the phenotype of the knockout animal of claim 16.

20. A method for selecting a potential therapeutic compound for use in the treatment of a disease state associated with a pain disorder comprising: d) administering the compound to a wild-type animal or an animal having a disease state associated with a pain disorder; e) measuring the resulting phenotype of wild-type animal or the animal having the disease state; and f) comparing the resulting pheontype of the wild-type animal or the animal having the disease state to the phenotype of the knockout animal of claim 17.

L15 ANSWER 9 OF 10 USPATFULL on STN
2002:81468 Modulation of human mast cell activation.
Pelleg, Amir, Haverford, PA, United States
Schulman, Edward S., Philadelphia, PA, United States

Duska Scientific Co., Haverford, PA, United States (U.S. corporation)
US 6372724 B1 20020416
WO 9842353 19981001
APPLICATION: US 1999-381692 19991202 (9)
WO 1998-US5922 19980324 19991202 PCT 371 date
PRIORITY: US 1997-41461P 19970325 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

CLM What is claimed is:

1. A method for modulating histamine release from stimulated human mast cells comprising contacting said cells with an effective amount of an agent which inhibits ATP binding to **P2-purinoceptors** on said cells.

2. A method according to claim 1 wherein the agent inhibits ATP binding to a **P2Y-purinoceptor** on said cells.

3. A method according to claim 2 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$ on said cells.

4. A method according to claim 2 wherein the agent is a **P2Y-purinoceptor antagonist**.

5. A method according to claim 2 wherein the agent is an allosteric modifier of a **P2Y-purinoceptor**.

6. A method according to claim 3 wherein the agent is a $P2Y_{1}$- or $P2Y_{2\text{-purinoceptor}}$ **antagonist**.

7. A method according to claim 6 wherein the **antagonist** is selected from the group consisting of adenosine-3'-phosphate-5'-phosphate, adenosine-3'-phosphate-5'-phosphosulfate, and a combination thereof.

8. A method according to claim 3 wherein the agent is an allosteric modifier of the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$.

9. A method according to claim 1 wherein the stimulated mast cells comprise immunologically stimulated mast cells.

10. A method according to claim 9 wherein the immunologically stimulated mast cells comprise lung, nose, eye, gut or joint mast cells.

11. A method according to claim 10 wherein the immunologically stimulated mast cells comprise lung mast cells.

12. A method according to claim 11 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$ on said immunologically stimulated lung mast cells.

13. A method for treating a human subject for a disorder characterized by undesirable release of histamine from immunologically stimulated lung mast cells comprising administering to the subject an effective amount of an agent which inhibits ATP binding to **P2-purinoceptors** on said mast cells.

14. A method according to claim 13 wherein the agent inhibits ATP binding to a **P2Y-purinoceptor** on said mast cells.

15. A method according to claim 14 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or the $P2Y_{2\text{-purinoceptor}}$ on said mast cells.

16. A method according to claim 15 wherein the agent is a $P2Y_{1}$- or $P2Y_{2\text{-purinoceptor}}$ **antagonist**.

17. A method according to claim 16 wherein the **antagonist** is selected from the group consisting of adenosine-3'-phosphate-5'-phosphate, adenosine-30'-phosphate-5'-phosphosulfate, and combinations thereof.

18. A method according to claim 13 wherein the disorder is an allergy.

19. A method according to claim 13 wherein the disorder is asthma.

20. A method according to claim 13 wherein the disorder is inflammatory lung disease.

21. A method for treating a human subject for a bronchoconstriction caused by histamine release from stimulated lung mast cells comprising administering to the subject an effective amount of an agent which inhibits ATP binding to **P2-purinoceptors** on said mast cells.

22. A method according to claim 21 wherein the agent inhibits ATP binding to a **P2Y-purinoceptor** on said mast cells.

23. A method according to claim 22 wherein the agent inhibits ATP binding to the $P2Y_{1\text{-purinoceptor}}$ or $P2Y_{2\text{-purinoceptor}}$ on said mast cells.

L15 ANSWER 10 OF 10 USPATFULL on STN
2002:48606 Irrigation solution and method for inhibition of pain and inflammation.
Demopulos, Gregory A., Mercer Island, WA, UNITED STATES
Pierce-Palmer, Pamela, San Francisco, CA, UNITED STATES
Herz, Jeffrey M., Mill Creek, WA, UNITED STATES
Omeros Medical Systems (U.S. corporation)
US 2002028798 A1 20020307
APPLICATION: US 2001-839633 A1 20010420 (9)
PRIORITY: US 1998-105026P 19981020 (60)
US 1998-105029P 19981020 (60)
US 1998-105044P 19981020 (60)
US 1998-105166P 19981021 (60)
US 1998-107256P 19981105 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of preemptively inhibiting pain and inflammation at a wound during a surgical procedure, comprising delivering to a wound during a surgical procedure a solution comprising at least one pharmacological agent selected from the group consisting of a mitogen-activated protein kinase (MAPK) inhibitor, an $\alpha_{2\text{-receptor}}$ agonist, a neuronal nicotinic acetylcholine receptor agonist, a cyclooxygenase-2 (COX-2) inhibitor, a soluble receptor and mixtures thereof, wherein the solution is applied locally and perioperatively to the surgical site.

2. The method of claim 1, wherein the pharmacological agent is a MAPK inhibitor selected from the group consisting of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)-1H-imidazole, [4-(3-iodophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)-1H-imidazole], [4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4- pyridyl)-1H-imidazole], [4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole], and 2'-Amino-3'-methoxyflavone.

3. The method of claim 1, wherein the pharmacological agent is an $\alpha_{2\text{-receptor}}$ agonist selected from the group consisting of clonidine; dexmedetomidine; oxymetazonline; (R)-(-)-3'-(2-amino-1-hydroxyethyl)-4'-fluoro-methanesulfoanilide (NS-49); 2-[(5-methylbenz-1-ox-4-azin-6-yl)imino]imidazoline (AGN-193080); AGN 191103; AGN 192172; 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (UKI4304); 5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo [4,5-d]azepin-2-amine (BHT920); 6-ethyl-5,6,7,8-tetrahydro-4H-oxaazolo[4,5-d]azepin-2-amine (BHT933); and 5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphyl-imidazoline (A-54741).

4. The method of claim 1, wherein the pharmacological agent is a neuronal nicotinic acetylcholine receptor agonist selected from the group consisting of (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594); (S)-5-(2-azetidinyl- methoxy)-2-chloropyridine (S-enatiomer of ABT-594); 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine (ABT-089); (R)-5-(2-Azetidinylmethoxy)-2-chloropyridine (ABT-594); (2,4)-Dimethoxy-benzylidene anabaseine (GTS-21); SBI-1765F; RJR-2403; 3-((1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine (A-84543); 3-(2(S)-azetidinylmethoxy)pyridine (A-85380); (+)-anatoxin-A and (-)anatoxin-A (1R)-1-(9-Azabicyclo [4.2.2]non-2-en-2-yl)-ethanoate fumarate, and (R,S)-3-pyridyl-1-methyl-2-(3-pyridyl)azetidine (MPA).

5. The method of claim 1, wherein the pharmacological agent is a COX-2 inhibitor selected from the group consisting of celecoxib, meloxicam, nimesulide, nimesulide, diclofenac, flosulide, N-[2-(cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)-phenyl]pyrazole, DuP 697, SC-58451,

RS-57067, SC-57666 and L-745,337.

6. The method of claim 1, wherein the pharmacological agent is a soluble receptor selected from the group consisting of tumor necrosis factor (TNF) soluble receptors, interleukin-1 (IL-1) cytokine receptors, class I cytokine receptors, and receptor tyrosine kinases.

7. The method of claim 1, wherein the solution further comprises at least one additional pain/inflammation inhibitory agent selected to act on a different molecular target than the pharmacological agent.

8. The method of claim 1, comprising continuously applying the solution to the wound.

9. The method of claim 8, comprising continuously irrigating the wound with the solution.

10. The method of claim 1, wherein the solution is applied by irrigation of the wound.

11. The method of claim 1, wherein the perioperative application of the solution comprises intraprocedural application together with preprocedural or postprocedural application of the solution.

12. The method of claim 1, wherein the perioperative application of the solution comprises preprocedural, intraprocedural and postprocedural application of the solution.

13. The method of claim 1, wherein each of the pharmacological agent in the solution is delivered locally at a concentration of no greater than 100,000 nanomolar.

14. The method of claim 7, wherein the at least one additional pain/inflammation inhibitory agent is selected from the group consisting of: serotonin receptor **antagonists**; serotonin receptor agonists; histamine receptor **antagonists**; bradykinin receptor **antagonists**; kallikrein inhibitors; tachykinin receptor **antagonists** including neurokinin$_1$ receptor subtype **antagonists** and neurokinin$_2$ receptor subtype **antagonists**; calcitonin gene-related peptide receptor **antagonists**; interleukin receptor **antagonists**; phospholipase inhibitors including PLA_2 isoform inhibitors and PLC_γ isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor **antagonists** including eicosanoid EP-1 receptor subtype **antagonists** and eicosanoid EP-4 receptor subtype **antagonists** and thromboxane receptor subtype **antagonists**; leukotriene receptor **antagonists** including leukotriene B_4 receptor subtype **antagonists** and leukotriene D_4 receptor subtype **antagonists**; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinoceptor agonists and **antagonists** including P_{2Y} receptor agonists and **P2X receptor antagonists**; and ATP-sensitive potassium channel openers.

15. A solution for use in the preemptive inhibition of pain and inflarnmation at a wound during a surgical procedure, comprising at least one pharmacological agent selected from the group consisting of a mitogen-activated protein kinase (MAPK) inhibitor, an $\alpha_{2\text{-receptor}}$ agonist, a neuronal nicotinic acetylcholine receptor agonist, a cyclooxygenase-2 (COX-2) inhibitor, a soluble receptor and mixtures thereof, in a liquid carrier, the concentration of said pharmacological agent within the solution being the concentration of that agent which is desired to be delivered locally, in the absence of metabolic transformation, to a wound in order to achieve a predetermined level of inhibitory effect at the wound.

16. The solution of claim 16, wherein the pharmacological agent is selected from the group consisting of 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)-1H-imidazole, [4-(3-iodophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-mirdazole], [4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4- pyridyl)-1H-imidazole], [4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-irnidazole], 2'-Amino-3'-methoxyflavone, clonidine; dexmedetomidine; oxymetazonline; (R)-(-)-3'-(2-amino-1-hydroxyethyl)-4'-fluoro-methanesulfoanilide (NS-49); 2-[(5-methylbenz-1-ox-4-azin-6-yl)imino]imidazoline (AGN-193080); AGN 191103; AGN 192172; 5-bromo-N-(4,5-dihydro-1H-imidazol-

2-yl)-6-quinoxalinamine (UK14304); 5,6,7,8-tetrahydro-6-(2-propenyl)-4H-thiazolo [4,5-d]azepin-2-amine (BHT920); 6-ethyl-5,6,7,8-tetrahydro-4H-oxaazolo[4,5-d]azepin-2-amine (BHT933); 5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphyl-imidazoline (A-54741), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594); (S)-5-(2-azetidinyl-methoxy)-2-chloropyridine (S-enatiomer of ABT-594); 2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine (ABT-089); (R)-5-(2-Azetidinylmethoxy)-2-chloropyridine (ABT-594); (2,4)-Dimethoxy-benzylidene anabaseine (GTS-21); SBI-1765F; RJR-2403; 3-((1-methyl-2(S)-pyrrolidinyl)methoxy)pyridine (A-84543); 3-(2(S)-azetidinylmethoxy)pyridine (A-85380); (+)-anatoxin-A and (-)anatoxin-A (IR)- 1 -(9-Azabicyclo [4.2.2]non-2-en-2-yl)-ethanoate fumarate, (R,S)-3-pyridyl-1-methyl-2-(3-pyridyl)azetidine (MPA), celecoxib, meloxicam, nimesulide, nimesulide, diclofenac, flosulide, N-[2-(cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide, 1-[(4-methylsulfonyl)phenyl]-3-trifluoromethyl-5-[(4-fluoro)phenyl]pyrazole, DuP 697, SC-58451, RS-57067, SC-57666, L-745,337, tumor necrosis factor (TNF) soluble receptors, interleukin-1 (IL-1) cytokine receptors, class I cytokine receptors, receptor tyrosine kinases and mixtures thereof.

17. The solution of claim 15, which further comprises at least one additional pain/inflammation inhibitory agent selected to act on a different molecular target than the at least one pharmacological agent.

18. The solution of claim 17, wherein the pharmacological agent and each of the additional pain/inflammation inhibitory agents in the solution is included at a concentration of no greater than 100,000 nanomolar, adjusted for dilution in the absence of metabolic transformation, at an intended local delivery site.

19. The solution of claim 17, wherein the at lease one additional pain/inflammation inhibitory agents are selected from the group consisting of serotonin receptor **antagonists**; serotonin receptor agonists; histamine receptor **antagonists**; bradykinin receptor **antagonists**; kallikrein inhibitors; tachykinin receptor **antagonists** including neurokinin, receptor subtype **antagonists** and neurokinin$_2$ receptor subtype **antagonists**; calcitonin gene-related peptide receptor **antagonists**; interleukin receptor **antagonists**; phospholipase inhibitors including PLA_2 isoform inhibitors and PLC, isoform inhibitors; cyclooxygenase inhibitors; lipooxygenase inhibitors; prostanoid receptor **antagonists** including eicosanoid EP-1 receptor subtype **antagonists** and eicosanoid EP-4 receptor subtype **antagonists** and thromboxane receptor subtype **antagonists**; leukotriene receptor **antagonists** including leukotriene B_4 receptor subtype **antagonists** and leukotriene D_4 receptor subtype **antagonists**; opioid receptor agonists including μ-opioid receptor subtype agonists, δ-opioid receptor subtype agonists, and κ-opioid receptor subtype agonists; purinoceptor agonists and **antagonists** including P_{2Y} receptor agonists and P_{2X} receptor **antagonists**; and ATP-sensitive potassium channel openers.

```
=> f
ENTER LOGIC EXPRESSION, QUERY NAME, OR (END):file wpids
        241469 FILE
            14 WPIDS
L16          1 FILE WPIDS
                 (FILE(W)WPIDS).

=> file wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     200.80     294.00

FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
COPYRIGHT (C) 2007 THE THOMSON CORPORATION

FILE LAST UPDATED:                        2 JAN 2007   <20070102/UP>
MOST RECENT THOMSON SCIENTIFIC UPDATE:     200701       <200701/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> YOU ARE IN THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX <<<

>>> IPC Reform reclassification data for the backfile is being
```

loaded into the database during the first half of January 2007.
There will not be any update date (UP) written for the reclassified
documents, but they can be identified by 20060101/UPIC. <<<

FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf

>>> FOR DETAILS ON THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX
PLEASE SEE
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

```
=> s (A1 adenosine receptor? or A1 receptor?)
         63413 A1
          7133 ADENOSINE
         61380 RECEPTOR?
            78 A1 ADENOSINE RECEPTOR?
                  (A1(W)ADENOSINE(W)RECEPTOR?)
         63413 A1
         61380 RECEPTOR?
           163 A1 RECEPTOR?
                  (A1(W)RECEPTOR?)
L17        214 (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)

=> s l17 and antagonist?
         40409 ANTAGONIST?
L18        123 L17 AND ANTAGONIST?

=> s l18 and py<2002
      10859312 PY<2002
                  (PY<2002)
L19         62 L18 AND PY<2002

=> s l19 and (HIV or human immunodeficiency virus or ADA or adenosine deaminase deficiency)
         23696 HIV
        202529 HUMAN
          8418 IMMUNODEFICIENCY
         48412 VIRUS
          5261 HUMAN IMMUNODEFICIENCY VIRUS
                  (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
           492 ADA
          7133 ADENOSINE
          1244 DEAMINASE
         13052 DEFICIENCY
            91 ADENOSINE DEAMINASE DEFICIENCY
                  (ADENOSINE(W)DEAMINASE(W)DEFICIENCY)
L20          0 L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOSINE
                  DEAMINASE DEFICIENCY)

=> d l19,bib,ab,1-5

L19  ANSWER 1 OF 62  WPIDS COPYRIGHT 2007       THE THOMSON CORP on
Full Text
     STN
AN   2001-605350 [69]   WPIDS
DNC  C2001-179647 [69]
TI   New pyrazolo-pyridine compound or its salt, useful for treating and
     preventing diseases such as seizure, ischemic angina, bronchial asthma,
     gout, diabetes mellitus, ulcer, meniere's syndrome and Parkinson's disease
DC   B02
IN   AKAHA A; ITANI H; KURODA S
PA   (FUJI-C) FUJISAWA PHARM CO LTD
CYC  1
PIA  JP 2001192384   A  20010717 (200169)* JA  22[0]
ADT  JP 2001192384 A JP 2000-378350 20001213
```

PRAI AU 1999-4622 19991213
AB JP 2001192384 A UPAB: 20050526
NOVELTY - Pyrazolo-pyridine compound (I) or its salt, is new.
DETAILED DESCRIPTION - Pyrazolo-pyridine compound or its salt of formula (I), is new.
R = Lower alkenyl, aryl-substituted lower alkyl or -A-R1, where the lower alkyl is optionally interrupted for an oxygen atom;
R1 = oxadiazolyl, thiazolyl, oxazolyl or imidozolyl, substituted with lower alkyl, acyl, aryl, pyridyl and/or trihalomethyl; and
A = lower alkylene.
INDEPENDENT CLAIMS are also included for:
(1) use of pyrazolo-pyridine compound or its salt in pharmaceuticals as adenosine **antagonist**;
(2) manufacture of pharmaceutical composition which involves mixing pyrazolo-pyridine compound (I) or its salt with a carrier; and
(3) evaluation of adenosine antagonism of pyrazolo-pyridine compound or its salt.
ACTIVITY - Anti-anginal; anti-asthmatic; anti-gout; immuno-stimulant; anti-diabetic; anti-ulcer; anti-inflammatory; auditory; anti-anemic; cardiant; thrombolytic; anti-parkinsonian; cerebro-protective; laxative; nootropic; anti-depressant; tranquilizer; hypotensive; anti-arrhythmic. No relevant biological data included.
MECHANISM OF ACTION - Adenosine **antagonist**; A1 and A2 receptor dual **antagonist** (claimed). The adenosine **antagonistic** activity of 3-(2-allyl-3-oxo-2,3-di hydro pyridazine-6-yl)-2-phenyl pyrazolo (1,5-a) pyridine (Ic) was examined using human **A1 receptor** by radiation coupling method. The result showed 0.04 nM of **antagonistic** activity.
USE - As pharmaceutical composition for preventing and treating ischemic seizure, ischemic angina, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immuno-suppression, diabetes mellitus, ulcer, pancreatic inflammation, meniere's syndrome, anemia, intestinal disease, ileus, cardiac infarction, thrombosis, obstruction, obstructive arteriosclerosis, thrombosis phlebitis, cerebral infarction and transience, depression, dementia, Parkinson's disease, anxiety, pain, cerebro-vascular disease, cardiac failure, hypertension, circulation insufficiency, contraction insufficiency, bradycardia type arrhythmia, electro-chemical malfunction (electro-mechanical dissociation), heart's blood line moving insufficiency (hemodynamic collapse), SIRS (systemic inflammatory response syndrome), multiple organ failures, renal insufficiency, kidney toxicity, nephrosis, nephritis, and edema (all claimed).
ADVANTAGE - None given.

L19 ANSWER 2 OF 62 WPIDS COPYRIGHT 2007 THE THOMSON CORP on Full Text
STN
AN 2001-582038 [65] WPIDS
DNC C2001-172557 [65]
TI New 2-adenosine thioether compounds useful as A2A receptor agonists, for stimulating coronary vasodilation, in angioplasty and as antiinflammatory, platelet aggregation inhibitor and platelet and neutrophil activation inhibitor compounds
DC B02
IN CRISTALLI G
PA (CRIS-I) CRISTALLI G; (CVTH-N) CV THERAPEUTICS INC
CYC 92
PIA WO 2001062768 A1 20010830 (200165)* EN 37[0]
AU 2001047227 A 20010903 (200202) EN
US 20010051612 A1 20011213 (200204) EN
ADT WO 2001062768 A1 WO 2001-US5854 20010222; US 20010051612 A1 Provisional US 2000-184475P 20000223; US 20010051612 A1 US 2000-733196 20001208; AU 2001047227 A AU 2001-47227 20010222
FDT AU 2001047227 A Based on WO 2001062768 A
PRAI US 2000-733196 20001208
US 2000-184475P 20000223
AB WO 2001062768 A1 UPAB: 20050526
NOVELTY - New 2-adenosine thioether compounds useful as A-2A receptor agonists are disclosed.
DETAILED DESCRIPTION - 2-Adenosine thioether compounds of formula (I) are new.
R1 = -CH2OH or -C(=O)NR7R8;
R2 = 1-15C alkyl, aryl, or heteroaryl each optionally substituted with 1-2 substituents selected from halo, NO2, heterocyclyl, aryl, heteroaryl, CF3, CN, OR20, SR20, N(R20)2, S(O)R22, SO2R22, SO2N(R20)2, SO2NR20COR22, SO2NR20CO2R22, SO2NR20CON(R20)2, NR20COR22, NR20CO2R22,

NR2OCON(R20)2, NR2OC(NR20)NHR23, COR20, CO2R20, CON(R20)2, and each optional heteroaryl, aryl, or heterocyclyl substitution is further optionally substituted with halo, alkyl, CF3, amino, mono- or di-alkylamino, SR20, S(O)R22, SO2R22, SO2N(R20)2, CN or OR20;

R7, R8 = H, or 1-6C alkyl optionally substituted with 1 substituent selected from aryl or heteroaryl;

R20 = H or 1-6C alkyl, aryl or heteroaryl, each optionally substituted with 1-2 substituents selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-1-6C alkyl, or CF3; and

R22 = 1-6C alkyl, aryl or heteroaryl, each optionally substituted with 1-2 substituents selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-(1-6C alkyl), or CF3.

ACTIVITY - Vasodilatory; Cardiant; Antiinflammatory; Vasotropic; Anticoagulant; Immunosuppressive; Cardioprotective.

MECHANISM OF ACTION - Adenosine A2A receptor agonists. The compounds were assayed to determine their affinity for the A2A receptor in a pig striatum membrane preparation. 0.2 mg of pig striatal membranes were treated with adenosine deaminase and 50 mM Tris buffer (pH=7.4) followed by mixing. To the pig membranes was added 2 microl of serially diluted DMSO stock solution of the compounds at concentrations of 100 microM to 10 nM or the control received 2 microl of DMSO alone, then the tritiated **antagonist** ZM 241385 in Tris buffer (50 mM, pH 7.4) was added to give a final concentration of 2 nM. After incubation at 23 degrees C for 2 hours, the solutions were filtered using a membrane harvester using multiple washing of the membranes (3x). The filter disks were counted in scintillation cocktail affording the amount of displacement of tritiated ZM by the competitive binding compositions. Greater than a 5 point curve was used to generate IC50 values. The Chang-Prusoff equation was used to generate Ki's from the IC50 data. The results showed that ((2S, 3S, 4R, 5R)-5-(6-amino-2-(phenylethylthio)purin-9-yl)-3,4-dihydroxyoxolan-2-yl)-N-ethylcarboxamide had Ki = 85 nM for the A2A receptor and Ki at least 10000nM for the **A1 receptor**.

USE - (I) can be used for stimulating coronary vasodilation by administration to stress the heart and induce a coronary steal situation for the purposes of imaging the heart (claimed). They can be used as an antiinflammatory, in adjunctive therapy with angioplasty, as a platelet aggregation inhibitor, and as an inhibitor of platelet and neutrophil activation (claimed). They can be used in heart imaging to identify mammals, and especially humans who are suffering from coronary disorders such as poor coronary perfusion which is indicative of coronary artery disease (CAD). The A2A agonists are effective against no-reflow by preventing neutrophil and platelet activation (e.g. they are believed to prevent release of superoxide from neutrophils), and are also useful as cardioprotective agents through their antiinflammatory action on neutrophils. Thus they are useful in situations when the heart will go through an ischemic state such as a transplant.

ADVANTAGE - The compounds are A2A agonists that provide specific activation of adenosine A2A receptors in the coronary vessels as opposed to adenosine **A1 receptors** in the atrium and AV-node and/or A2B receptors in peripheral vessels, thus avoiding undesirable side-effects.

L19 ANSWER 3 OF 62 WPIDS COPYRIGHT 2007 THE THOMSON CORP on
Full Text
STN
AN 2001-441477 [47] WPIDS
DNC C2001-133322 [47]
TI New pyrazolopyrazine compound and its salt useful as medicaments for treating ulcer, edema, anemia etc.
DC B02
IN AKAHANE A; AKAHANE A F P C L; ITANI H; ITANI H F P C L; KURODA S; KURODA S F P C L; MATSUOKA H; MATSUOKA H F P C L; MATSUOKA N; MATSUOKA N F P C L; OKU T; OKU T F P C L; SATO Y; SATO Y F P C L; TABUCHI S; TABUCHI S F P C L; TADA M; TADA M F P C L; TANAKA A; TANAKA A F P C L
PA (FUJI-C) FUJISAWA PHARM CO LTD
CYC 92
PIA WO 2001040230 A1 20010607 (200147)* EN 69[0]
AU 2001013093 A 20010612 (200154) EN
EP 1244669 A1 20021002 (200265) EN
JP 2003515537 W 20030507 (200331) JA 75
ADT WO 2001040230 A1 WO 2000-JP8008 20001113; EP 1244669 A1 EP 2000-974973 20001113; EP 1244669 A1 WO 2000-JP8008 20001113; JP 2003515537 W WO 2000-JP8008 20001113; AU 2001013093 A AU 2001-13093 20001113; JP 2003515537 W JP 2001-540985 20001113
FDT AU 2001013093 A Based on WO 2001040230 A; EP 1244669 A1 Based on WO

2001040230 A; JP 2003515537 W Based on WO 2001040230 A
PRAI AU 1999-4414 19991202
AB WO 2001040230 A1 UPAB: 20050526
NOVELTY - A pyrazolopyrazine compound (I) or its salt is new.
DETAILED DESCRIPTION - A pyrazolopyrazine compound of formula (I) or its salt is new.
R1 = aryl optionally substituted by 1 or more substituents; and
R2 = H, lower alkyl, lower alkenyl, cyclo(lower)alkyl, heteromonocyclic group or lower alkyl substituted with at least one of cyclo(lower)alkyl, halo, cyano, aryl or heteromonocylic group.
INDEPENDENT CLAIMS are also included for the following:
(1) preparation of (I) or its salt; and
(2) preparation of a pharmaceutical composition by mixing (I) or its salt with a carrier.
ACTIVITY - Tranquilizer; Antiasthmatic; Antianemic; Antianginal; Antiarteriosclerotic; Laxative; Nootropic; Antidepressant; Antidiabetic; Antiinflammatory; Antigout; Cardiant; Hypotensive; Hypertensive; Vasotropic; Auditory; Anorectic; Antiparkinsonian; Analgesic; Antiinflammatory; Anticoagulant; Thrombolytic; Antiulcer; Neuroprotective; and Cerebroprotective.
MECHANISM OF ACTION - An adenosine **antagonist** (preferably **A1 receptor** and A2) (particularly A2a) receptor dual agonists).
3-(2-Ethyl-3-oxo-2,3-dihydropyridazin-6-yl)-2-phenyl pyrazolo(1,5-a)pyrazine (3.2 mg/kg) was administered orally to 7 mice. Then, haloperidol (0.32 mg/kg) was injected intraperitoneally 30 minutes after the administration of the compound. After the injection, the cataleptic responses of mice were measured. A manifestation rate of catalepsy in 7 mice was 1/7.
USE - As a medicament for preventing or treating a disease such as depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris; as an adenosine **antagonist** (preferably an **A1 receptor** and A2 receptor dual **antagonists**); for the production of a pharmaceutical composition for the therapy of diseases on which an adenosine **antagonist** is therapeutically effective and for evaluation of adenosine antagonim (all claimed).
ADVANTAGE - The pyrazolopyrazine compound and its salt are adenosine **antagonists** (especially, **A1 receptor** and A2 (particularly A2a) receptor dual **antagonists**) and possess various pharmacological actions such as anticatalepsy action, cognitive enhancing action, analgesic action, locomotor action, antidepressant action, diuretic action, cardioprotective action, cardiotonic action, vasodilating action (e.g. cerebral vasodilating action), the action of increasing the renal blood flow, renal protective action, improvement action of renal function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin release, the action of increasing the production of erythropoietin and inhibiting action of platelet aggregation.

L19 ANSWER 4 OF 62 WPIDS COPYRIGHT 2007 THE THOMSON CORP on Full Text
STN
AN 2001-441456 [47] WPIDS
CR 2000-147035
DNC C2001-133305 [47]
TI New heterocyclic compounds are adenosine A1, A2a and A3 receptor **antagonists**, for treating e.g. respiratory, opthalmological, inflammatory, neurological and gastrointestinal disorders and cancer
DC B02; B05; C02; C03
IN CASTELHANO A; CASTELHANO A L; MCKIBBEN B; WITTER D; WITTER D J; CASTELHANO L; WITTER J
PA (OSIP-N) OSI PHARM INC
CYC 93
PIA WO 2001039777 A1 20010607 (200147)* EN 368[0]
AU 2001024270 A 20010612 (200154) EN
EP 1246623 A1 20021009 (200267) EN

KR 2002064327 A 20020807 (200309) KO
JP 2003519102 W 20030617 (200349) JA 328
MX 2002005357 A1 20030501 (200415) ES
ZA 2002004153 A 20041124 (200481) EN 627
US 6878716 B1 20050412 (200525) EN
MX 231400 B 20051013 (200620) ES
EP 1246623 B1 20060809 (200654) EN
DE 60030002 E 20060921 (200663) DE
EP 1731520 A1 20061213 (200701) EN

ADT WO 2001039777 A1 WO 2000-US32702 20001201; US 6878716 B1 Provisional US 1998-87702P 19980602; US 6878716 B1 Provisional US 1999-123216P 19990308; US 6878716 B1 Provisional US 1999-126527P 19990326; US 6878716 B1 CIP of WO 1999-US12135 19990601; US 6878716 B1 US 1999-454074 19991202; DE 60030002 E DE 2000-630002 20001201; EP 1246623 A1 EP 2000-988011 20001201; EP 1246623 B1 EP 2000-988011 20001201; DE 60030002 E EP 2000-988011 20001201; EP 1246623 A1 WO 2000-US32702 20001201; JP 2003519102 W WO 2000-US32702 20001201; MX 2002005357 A1 WO 2000-US32702 20001201; MX 231400 B WO 2000-US32702 20001201; EP 1246623 B1 WO 2000-US32702 20001201; DE 60030002 E WO 2000-US32702 20001201; AU 2001024270 A AU 2001-24270 20001201; JP 2003519102 W JP 2001-541509 20001201; ZA 2002004153 A ZA 2002-4153 20020524; MX 2002005357 A1 MX 2002-5357 20020529; MX 231400 B MX 2002-5357 20020529; KR 2002064327 A KR 2002-707039 20020531; EP 1731520 A1 Div Ex EP 2000-988011 20001201; EP 1731520 A1 EP 2006-16543 20001201

FDT DE 60030002 E Based on EP 1246623 A; AU 2001024270 A Based on WO 2001039777 A; EP 1246623 A1 Based on WO 2001039777 A; JP 2003519102 W Based on WO 2001039777 A; MX 2002005357 A1 Based on WO 2001039777 A; MX 231400 B Based on WO 2001039777 A; EP 1246623 B1 Based on WO 2001039777 A; DE 60030002 E Based on WO 2001039777 A; EP 1731520 A1 Div ex EP 1246623 A

PRAI US 1999-454074 19991202
US 1999-454075 19991202
US 1999-454254 19991202
US 1998-87702P 19980602
US 1999-123216P 19990308
US 1999-126527P 19990326
WO 1999-US12135 19990601

AB WO 2001039777 A1 UPAB: 20060117

NOVELTY - Bicyclic compounds (VI)-(X) are new.

DETAILED DESCRIPTION - Bicyclic compounds of formula (VI)-(X) are new.

R2 = 5-6 membered aromatic ring;

R3, R4 = H or alkyl; and

X = O or S;

provided that in (VII), R2 is not 4-pyridyl.

INDEPENDENT CLAIMS are also included for:

(1) a water-soluble prodrug of (VI)-(X) that is metabolized in vivo to produce an active drug that selectively inhibits the **A1 adenosine receptor**;

(2) a combination therapy for asthma comprising (VI)-(X), a steroid, a beta2 agonist, glucocorticoid steroid, leucotriene **antagonist** or anticholinergic agonist;

(3) a packaged pharmaceutical composition for treating a disease associated with the **A1 adenosine receptor**, comprising a container containing (VI)-(X), and instructions for using the compound(s) for treating the disease;

(4) preparation of (VI)-(X);

(5) a compound of formula (XI);

(6) a compound of formula (XII);

(7) a water-soluble prodrug of (XI) or (XII) that is metabolized in vivo to produce an active drug that selectively inhibits the A2a adenosine receptor;

(8) a combination therapy for Parkinson's disease comprising (XI) or (XII) and a dopamine enhancer;

(9) a combination therapy for cancer comprising (XI) or (XII) and a cytotoxic agent;

(10) a combination therapy for glaucoma comprising (XI) or (XII), a prostaglandin agonist, muscarinic agonist or a beta2 **antagonist**;

(11) a packaged pharmaceutical composition for treating a disease associated with the A2a adenosine receptor, comprising a container containing (XI) or (XII), and instructions for using the compound(s) for treating the disease;

(12) preparations of (XI) and (XII);

(13) compounds of formula (XIII)-(XV);

(14) a water-soluble prodrug of (XIII)-(XV) that is metabolized in vivo to produce an active drug that selectively inhibits the A3 adenosine

receptor;

(15) a combination therapy for glycoma comprising (XIII)-(XV), a prostaglandin agonist, beta2-2 agonist or muniscrinic agonist;

(16) a packaged pharmaceutical composition for treating a disease associated with the A3 adenosine receptor, comprising a container containing (XIII)-(XV), and instructions for using the compound(s) for treating the disease; and

(17) preparation of (XIII)-(XV).

NR11R12 = optionally substituted 4-8 membered ring;

Ar = optionally substituted 4-6 membered ring;

R14 = H, alkyl, arylalkyl, optionally substituted aryl, amino, -C(R8)(R9)XR6;

X = O, S or NR7;

R8, R9 = H or alkyl;

R6, R7 = alkyl or cycloalkyl; or

NR6R7 = optionally substituted 4-7 membered ring;

R15 = H, optionally substituted alkyl or cycloalkyl;

R = H or Me;

R21 = 3-hydroxy cyclopentyl ethylamino carbonylaminopropyl, N,N-diethylamino carbonylaminoethyl, thioacetamidoethyl, 3-amino acetyloxycyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonylaminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methylpropyl, 1-aminocarbonyl-2-phenylethyl, 3-hydroxy azetidino, 2-imidazolylethyl, acetamidoethyl, 1-(R)-phenyl-2-hydroxyethyl or N-methylaminocarbonyl pyridyl-2-methyl;

R23, R24 = H, aryl or optionally substituted alkyl;

NR31R32 = 3-hydroxy pyrrolidino, 3-methoxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino or 3-hydroxymethyl piperidino; and

R33, R34 = H, aryl or optionally substituted alkyl;

provided that NR11R12 is not 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methoxy carbonylmethyl pyrrolidino or 3-aminocarbonylmethyl pyrrolidino, and NR11R12 = 4-hydroxymethyl piperadino only when Ar = 4-pyridyl.

ACTIVITY - Antiasthmatic; antiinflammatory; antiallergic; anticoagulant; vasotropic; nootropic; neuroprotective; antiparkinsonian; dermatological; antipsoriatic; gastrointestinal; cardiant; antiulcer, cytostatic; hypotensive; cerebroprotective; antiarthritic; immunomodulator; antidiabetic; antianemic; antiinfertility; nephrotropic; opthalmological; immunoprotective; antidiarrheic.

MECHANISM OF ACTION - Adenosine **A1 receptor antagonist**; adenosine A2a receptor **antagonist**; adenosine A3 receptor **antagonist**; adenylate cyclase stimulator.

In assays to determine binding to adenosine receptors, 4-(2-N'-methylureaethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo(2,3-d)pyrimidine (VIa) had Ki values of 33, 58, 8.8 and 18 nM respectively for A1, A2a, A2b and A3 receptors.

USE - The compounds can be used to treat asthma, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory disorders, disorders associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, senile dementia, Parkinson's disease, renal failure, cardiac arrhythmias, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy, dromotropy, bronchoconstriction, neutropil chemotaxis, reflux condition, ulcerative colitis, hypersensitivity, hay fever, serum sickness, allergic vasculitis, atopic dermatitis, psoriasis, eczema, pulmonary fibrosis, chronic airway inflammation, hypereosinophilic syndromes, gastroenteritis, edema, urticaria, myocardial disease, eosinophilia, inflammatory bowel disease, carcinomas, granulomas, hypertension, mast cell degranulation, tumors, hypoxia, cerebral ischemia, diuresis, neurological disorder, myocardial ischemia, arthritis, autoimmune disease, Crohn's disease, Graves' disease, diabetes, multiple sclerosis, anemia, fertility disorders, lupus erythematosus, reperfusion injury, brain arteriole diameter, release of allergic mediatores, scleroderma, stroke, global ischemia, CNS disorder, cardiovascular disorder, renal disorder, eye disorders e.g. glaucoma, glycoma, damage to optic nerve or retinal head damage, and immunological disorders (all claimed).

L19 ANSWER 5 OF 62 WPIDS COPYRIGHT 2007 THE THOMSON CORP on
Full Text
STN
AN 2001-408066 [43] WPIDS
DNC C2001-123524 [43]
TI New polycycloalkylpurine derivatives are adenosine receptor **antagonists**

useful for treating, e.g. cardiac and circulatory disorders, degenerative disorders of the central nervous system, respiratory disorders and depression

DC B02

IN CHANG H X; DOWLING J E; ENSINGER C I; ENSINGER C L; KIESMAN W F; KUMARAVEL G; LIN K C; PETTER R C; XI C H

PA (BIOJ-C) BIOGEN INC; (CHAN-I) CHANG H X; (DOWL-I) DOWLING J E; (ENSI-I) ENSINGER C L; (KIES-I) KIESMAN W F; (KUMA-I) KUMARAVEL G; (LINK-I) LIN K C; (PETT-I) PETTER R C; (BIOJ-C) BIOGEN IDEC MA INC

CYC 93

PIA	**WO 2001034610**	**A1**	**20010517 (200143)***	**EN**	**124[19]**	
	AU 2001016000	**A**	**20010606 (200152)**	**EN**		
	NO 2002002238	A	20020712 (200258)	NO		
	BR 2000015545	A	20020806 (200260)	PT		
	CZ 2002001614	A3	20020717 (200260)	CS		
	EP 1230243	A1	20020814 (200261)	EN		
	KR 2002049050	A	20020624 (200281)	KO		
	SK 2002000663	A3	20030204 (200318)	SK		
	HU 2002003369	A2	20030128 (200323)	HU		
	JP 2003513982	W	20030415 (200328)	JA	176	
	CN 1402729	A	20030312 (200339)	ZH		
	NZ 519426	A	20030829 (200365)	EN		
	US 6649600	B1	20031118 (200376)	EN		
	US 20040067966	A1	20040408 (200426)	EN		
	ZA 2002003701	A	20040428 (200432)	EN	151	
	NZ 527917	A	20050324 (200523)	EN		
	IN 2002000628	P2	20050311 (200579)	EN		
	US 20060252730	A1	20061109 (200674)	EN		
	AU 784556	B2	20060504 (200681)	EN		

ADT WO 2001034610 A1 WO 2000-US31058 20001113; US 6649600 B1 Provisional US 1999-165191P 19991112; US 20040067966 A1 Provisional US 1999-165191P 19991112; US 20060252730 A1 Provisional US 1999-165191P 19991112; BR 2000015545 A BR 2000-15545 20001113; CN 1402729 A CN 2000-816439 20001113; EP 1230243 A1 EP 2000-978546 20001113; NZ 519426 A NZ 2000-519426 20001113; NZ 527917 A Div Ex NZ 2000-519426 20001113; NZ 527917 A NZ 2000-527917 20001113; US 6649600 B1 US 2000-711543 20001113; US 20040067966 A1 Cont of US 2000-711543 20001113; US 20060252730 A1 Cont of US 2000-711543 20001113; NO 2002002238 A WO 2000-US31058 20001113; CZ 2002001614 A3 WO 2000-US31058 20001113; BR 2000015545 A WO 2000-US31058 20001113; EP 1230243 A1 WO 2000-US31058 20001113; SK 2002000663 A3 WO 2000-US31058 20001113; HU 2002003369 A2 WO 2000-US31058 20001113; JP 2003513982 W WO 2000-US31058 20001113; NZ 519426 A WO 2000-US31058 20001113; IN 2002000628 P2 WO 2000-US31058 20001113; AU 2001016000 A AU 2001-16000 20001113; JP 2003513982 W JP 2001-537323 20001113; CZ 2002001614 A3 CZ 2002-1614 20001113; HU 2002003369 A2 HU 2002-3369 20001113; SK 2002000663 A3 SK 2002-663 20001113; IN 2002000628 P2 IN 2002-KN628 20020508; ZA 2002003701 A ZA 2002-3701 20020509; NO 2002002238 A NO 2002-2238 20020510; KR 2002049050 A KR 2002-706093 20020511; US 20040067966 A1 US 2003-646454 20030821; US 20060252730 A1 Cont of US 2003-646454 20030821; US 20060252730 A1 US 2006-484805 20060710; AU 784556 B2 AU 2001-16000 20001113

FDT NZ 527917 A Div ex NZ 519426 A; US 20040067966 A1 Cont of US 6649600 B; US 20060252730 A1 Cont of US 6649600 B; AU 2001016000 A Based on WO 2001034610 A; CZ 2002001614 A3 Based on WO 2001034610 A; BR 2000015545 A Based on WO 2001034610 A; EP 1230243 A1 Based on WO 2001034610 A; SK 2002000663 A3 Based on WO 2001034610 A; HU 2002003369 A2 Based on WO 2001034610 A; JP 2003513982 W Based on WO 2001034610 A; NZ 519426 A Based on WO 2001034610 A; AU 784556 B2 Based on WO 2001034610 A

PRAI US 1999-165191P 19991112
US 2000-711543 20001113
US 2003-646454 20030821
US 2006-484805 20060710

AB WO 2001034610 A1 UPAB: 20060202

NOVELTY - Polycycloalkylpurine (I) derivatives, are new.

DETAILED DESCRIPTION - Polycycloalkylpurine derivatives of formula (I) are new.

R1, R2 = H or optionally substituted alkyl, alkenyl, alkynyl or aryl;

R3 = optionally substituted bi-, tri- or penta-cyclic group;

R6 = H, optionally substituted alkyl, acyl, alkylsulfonyl, optionally substituted aralkyl or heterocyclyl; and

X1, X2 = O or S.

Full definitions given in DEFINITION field.

INDEPENDENT CLAIMS are included for (i)

(1) compositions comprising (I);
(2) a method of treating conditions characterized by elevated adenosine levels and/or increased sensitivity to adenosine comprising administration of (I); and
(3) a method for preparing 8-substituted xanthines comprising protecting the N7-position of an N7,C8-dihydroxanthine, deprotonating the C8-position with a strong base, trapping the anion with a carboxyl, carbonyl, aldehyde or ketone and deprotecting the N7-position.
ACTIVITY - Cardiant; antiparkinsonian; antidepressant; cerebroprotective; tranquilizer; hepatotropic; antidiabetic; antiasthmatic; antiinflammatory; respiratory-general.
MECHANISM OF ACTION - Adenosine A1 inhibition. (I) showed rat A1 KI values of 0.6 to 434 nM and human A1 KI values of 1.6 to 1000 nM with an A2a/A1 of at least 10 and in one case 1000.
USE - (I) are useful for treating conditions characterized by elevated adenosine levels and/or increased sensitivity to adenosine, e.g. cardiac and circulatory disorders, degenerative disorders of the central nervous system, respiratory disorders, diseases for which diuretic treatment is indicated, Parkinson's disease, depression, traumatic brain damage, post-stroke neurological deficit, respiratory depression, neonatal brain trauma, dyslexia, hyperactivity, cystic fibrosis, cirrhotic ascites, neonatal apnea, renal failure, diabetes, asthma and edematous conditions.
ADVANTAGE - (I) are highly potent and selective inhibitors of adenosine **A1 receptors** and are easily manufactured.

```
=> d his

     (FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

     FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
                E WILSON CONSTANCE N/IN
L1               3 S E4

     FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
                E WILSON C N/IN
L2              19 S E3
L3               8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
                E WILSON C N/AU
L4              96 S E3
L5               1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6            2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7            1803 S L6 AND ANTAGONIST?
L8             319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9             140 S L8 AND ANTAGONIST?/CLM
L10             61 S L9 AND AY<2002
L11              4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12             57 S L10 NOT L11
L13              1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14             56 S L10 NOT (L11 OR L13)
L15             10 S L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)
L16              1 F FILE WPIDS

     FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
L17            214 S (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)
L18            123 S L17 AND ANTAGONIST?
L19             62 S L18 AND PY<2002
L20              0 S L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOS

=> s l19 and (immunolog?)
         16193 IMMUNOLOG?
L21          2 L19 AND (IMMUNOLOG?)

=> d l21,bib,ab,1-2

L21  ANSWER 1 OF 2  WPIDS COPYRIGHT 2007       THE THOMSON CORP on STN
Full Text
AN   2001-441456 [47]   WPIDS
CR   2000-147035
DNC  C2001-133305 [47]
TI   New heterocyclic compounds are adenosine A1, A2a and A3 receptor
```

antagonists, for treating e.g. respiratory, opthalmological, inflammatory, neurological and gastrointestinal disorders and cancer

DC B02; B05; C02; C03

IN CASTELHANO A; CASTELHANO A L; MCKIBBEN B; WITTER D; WITTER D J; CASTELHANO L; WITTER J

PA (OSIP-N) OSI PHARM INC

CYC 93

PIA	**WO 2001039777**	**A1**	**20010607 (200147)***	**EN**	**368[0]**
	AU 2001024270	**A**	**20010612 (200154)**	**EN**	
	EP 1246623	A1	20021009 (200267)	EN	
	KR 2002064327	A	20020807 (200309)	KO	
	JP 2003519102	W	20030617 (200349)	JA	328
	MX 2002005357	A1	20030501 (200415)	ES	
	ZA 2002004153	A	20041124 (200481)	EN	627
	US 6878716	B1	20050412 (200525)	EN	
	MX 231400	B	20051013 (200620)	ES	
	EP 1246623	B1	20060809 (200654)	EN	
	DE 60030002	E	20060921 (200663)	DE	
	EP 1731520	A1	20061213 (200701)	EN	

ADT WO 2001039777 A1 WO 2000-US32702 20001201; US 6878716 B1 Provisional US 1998-87702P 19980602; US 6878716 B1 Provisional US 1999-123216P 19990308; US 6878716 B1 Provisional US 1999-126527P 19990326; US 6878716 B1 CIP of WO 1999-US12135 19990601; US 6878716 B1 US 1999-454074 19991202; DE 60030002 E DE 2000-630002 20001201; EP 1246623 A1 EP 2000-988011 20001201; EP 1246623 B1 EP 2000-988011 20001201; DE 60030002 E EP 2000-988011 20001201; EP 1246623 A1 WO 2000-US32702 20001201; JP 2003519102 W WO 2000-US32702 20001201; MX 2002005357 A1 WO 2000-US32702 20001201; MX 231400 B WO 2000-US32702 20001201; EP 1246623 B1 WO 2000-US32702 20001201; DE 60030002 E WO 2000-US32702 20001201; AU 2001024270 A AU 2001-24270 20001201; JP 2003519102 W JP 2001-541509 20001201; ZA 2002004153 A ZA 2002-4153 20020524; MX 2002005357 A1 MX 2002-5357 20020529; MX 231400 B MX 2002-5357 20020529; KR 2002064327 A KR 2002-707039 20020531; EP 1731520 A1 Div Ex EP 2000-988011 20001201; EP 1731520 A1 EP 2006-16543 20001201

FDT DE 60030002 E Based on EP 1246623 A; AU 2001024270 A Based on WO 2001039777 A; EP 1246623 A1 Based on WO 2001039777 A; JP 2003519102 W Based on WO 2001039777 A; MX 2002005357 A1 Based on WO 2001039777 A; MX 231400 B Based on WO 2001039777 A; EP 1246623 B1 Based on WO 2001039777 A; DE 60030002 E Based on WO 2001039777 A; EP 1731520 A1 Div ex EP 1246623 A

PRAI US 1999-454074 19991202
US 1999-454075 19991202
US 1999-454254 19991202
US 1998-87702P 19980602
US 1999-123216P 19990308
US 1999-126527P 19990326
WO 1999-US12135 19990601

AB WO 2001039777 A1 UPAB: 20060117

NOVELTY - Bicyclic compounds (VI)-(X) are new.

DETAILED DESCRIPTION - Bicyclic compounds of formula (VI)-(X) are new.

R2 = 5-6 membered aromatic ring;

R3, R4 = H or alkyl; and

X = O or S;

provided that in (VII), R2 is not 4-pyridyl.

INDEPENDENT CLAIMS are also included for:

(1) a water-soluble prodrug of (VI)-(X) that is metabolized in vivo to produce an active drug that selectively inhibits the **A1 adenosine receptor**;

(2) a combination therapy for asthma comprising (VI)-(X), a steroid, a beta2 agonist, glucocorticoid steroid, leucotriene **antagonist** or anticholinergic agonist;

(3) a packaged pharmaceutical composition for treating a disease associated with the **A1 adenosine receptor**, comprising a container containing (VI)-(X), and instructions for using the compound(s) for treating the disease;

(4) preparation of (VI)-(X);

(5) a compound of formula (XI);

(6) a compound of formula (XII);

(7) a water-soluble prodrug of (XI) or (XII) that is metabolized in vivo to produce an active drug that selectively inhibits the A2a adenosine receptor;

(8) a combination therapy for Parkinson's disease comprising (XI) or (XII) and a dopamine enhancer;

(9) a combination therapy for cancer comprising (XI) or (XII) and a cytotoxic agent;

(10) a combination therapy for glaucoma comprising (XI) or (XII), a prostaglandin agonist, muscarinic agonist or a beta2 **antagonist**;

(11) a packaged pharmaceutical composition for treating a disease associated with the A2a adenosine receptor, comprising a container containing (XI) or (XII), and instructions for using the compound(s) for treating the disease;

(12) preparations of (XI) and (XII);

(13) compounds of formula (XIII)-(XV);

(14) a water-soluble prodrug of (XIII)-(XV) that is metabolized in vivo to produce an active drug that selectively inhibits the A3 adenosine receptor;

(15) a combination therapy for glycoma comprising (XIII)-(XV), a prostaglandin agonist, beta2-2 agonist or muniscrinic agonist;

(16) a packaged pharmaceutical composition for treating a disease associated with the A3 adenosine receptor, comprising a container containing (XIII)-(XV), and instructions for using the compound(s) for treating the disease; and

(17) preparation of (XIII)-(XV).

NR11R12 = optionally substituted 4-8 membered ring;

Ar = optionally substituted 4-6 membered ring;

R14 = H, alkyl, arylalkyl, optionally substituted aryl, amino, -C(R8)(R9)XR6;

X = O, S or NR7;

R8, R9 = H or alkyl;

R6, R7 = alkyl or cycloalkyl; or

NR6R7 = optionally substituted 4-7 membered ring;

R15 = H, optionally substituted alkyl or cycloalkyl;

R = H or Me;

R21 = 3-hydroxy cyclopentyl ethylamino carbonylaminopropyl, N,N-diethylamino carbonylaminoethyl, thioacetamidoethyl, 3-amino acetyloxycyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonylaminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methylpropyl, 1-aminocarbonyl-2-phenylethyl, 3-hydroxy azetidino, 2-imidazolylethyl, acetamidoethyl, 1-(R)-phenyl-2-hydroxyethyl or N-methylaminocarbonyl pyridyl-2-methyl;

R23, R24 = H, aryl or optionally substituted alkyl;

NR31R32 = 3-hydroxy pyrrolidino, 3-methoxy carbonylmethyl pyrrolidino, 3-aminocarbonylmethyl pyrrolidino or 3-hydroxymethyl piperidino; and

R33, R34 = H, aryl or optionally substituted alkyl;

provided that NR11R12 is not 3-acetamido piperadino, 3-hydroxy pyrrolidino, 3-methoxy carbonylmethyl pyrrolidino or 3-aminocarbonylmethyl pyrrolidino, and NR11R12 = 4-hydroxymethyl piperadino only when Ar = 4-pyridyl.

ACTIVITY - Antiasthmatic; antiinflammatory; antiallergic; anticoagulant; vasotropic; nootropic; neuroprotective; antiparkinsonian; dermatological; antipsoriatic; gastrointestinal; cardiant; antiulcer, cytostatic; hypotensive; cerebroprotective; antiarthritic; immunomodulator; antidiabetic; antianemic; antiinfertility; nephrotropic; opthalmological; immunoprotective; antidiarrheic.

MECHANISM OF ACTION - Adenosine **A1 receptor antagonist**; adenosine A2a receptor **antagonist**; adenosine A3 receptor **antagonist**; adenylate cyclase stimulator.

In assays to determine binding to adenosine receptors, 4-(2-N'-methylureaethyl)amino-6-(4-fluorophenoxy)methyl-2-phenyl-7H-pyrrolo(2,3-d)pyrimidine (VIa) had Ki values of 33, 58, 8.8 and 18 nM respectively for A1, A2a, A2b and A3 receptors.

USE - The compounds can be used to treat asthma, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory disorders, disorders associated with locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, senile dementia, Parkinson's disease, renal failure, cardiac arrhythmias, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy, dromotropy, bronchoconstriction, neutropil chemotaxis, reflux condition, ulcerative colitis, hypersensitivity, hay fever, serum sickness, allergic vasculitis, atopic dermatitis, psoriasis, eczema, pulmonary fibrosis, chronic airway inflammation, hypereosinophilic syndromes, gastroenteritis, edema, urticaria, myocardial disease, eosinophilia, inflammatory bowel disease, carcinomas, granulomas, hypertension, mast cell degranulation, tumors, hypoxia, cerebral ischemia, diuresis, neurological disorder, myocardial ischemia, arthritis, autoimmune disease, Crohn's disease, Graves' disease, diabetes, multiple sclerosis, anemia, fertility disorders, lupus erythematosus, reperfusion injury, brain arteriole diameter, release of allergic mediatores, scleroderma, stroke, global ischemia, CNS disorder, cardiovascular

disorder, renal disorder, eye disorders e.g. glaucoma, glycoma, damage to optic nerve or retinal head damage, and **immunological** disorders (all claimed).

L21 ANSWER 2 OF 2 WPIDS COPYRIGHT 2007 THE THOMSON CORP on STN
Full Text
AN 1985-310116 [49] WPIDS
DNC C1985-134241 [16]
TI Analogues of adenosine receptor ligands with functionalised chains - useful for treating cardiac conditions etc. and as high affinity labelled probes and in chromatographic materials
DC B02
IN DALY J W; JACOBSON K A; KIRK K L
PA (USSH-C) US DEPT OF HEALTH
CYC 1
PIA US 717624 A0 19850917 (198549)* EN 64[0]
ADT US 717624 A0 US 1985-717624 19850329
AB US 6717624 N UPAB: 20050426
Analogues of adenosine receptor ligands bearing functionalised chains are prepd. and are (a) attached covalently to organic cpds. such as amines and peptides, to give new biologically active prods. (I) or (b) used as receptor probes.

USE/ADVANTAGE - Adenosine is a neuromodulator in the circulatory, endocrine, immune and central nervous systems, with the 2 receptor sub-types A, (inhibiting towards adenylate cyclase) and A2 (stimulatory). The (I) are tested for adenosine agonist and **antagonist** activities. Typically 6-(p-carboxymethyl)phenyl) adenosine and its derivs. are synthesised and are functionalised agonists. The COOH when coupled to amines gives amino congeners as agonists having **A1-receptor** binding affinities in the nanomolar range. The **A1-receptor** mediates cardiac and central depressant and antilipolytic activities, and the A2-receptor is associated with inhibition of platelet aggregation, cardiovascular effect etc. Combinations of prods. to give a desired A1/A2 selective effect are prepd., e.g. for antihypertensive use. - The congeners are useful in the prepn. of high affinity receptor probes for use in histochemical and binding studies and radioactive, fluorescent or **immunological** labels are used. They may be insolubilised on polymers for use in affinity chromatography. For such uses a potent congener contains a terminal amidoethyleneamine function.

=> d his

(FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
E WILSON CONSTANCE N/IN
L1 3 S E4

FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
E WILSON C N/IN
L2 19 S E3
L3 8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
E WILSON C N/AU
L4 96 S E3
L5 1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6 2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7 1803 S L6 AND ANTAGONIST?
L8 319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9 140 S L8 AND ANTAGONIST?/CLM
L10 61 S L9 AND AY<2002
L11 4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12 57 S L10 NOT L11
L13 1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14 56 S L10 NOT (L11 OR L13)
L15 10 S L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)
L16 1 F FILE WPIDS

FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
L17 214 S (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)
L18 123 S L17 AND ANTAGONIST?

```
L19          62 S L18 AND PY<2002
L20           0 S L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOS
L21           2 S L19 AND (IMMUNOLOG?)

=> s l19 and (infect?)
         84500 INFECT?
L22           1 L19 AND (INFECT?)

=> d l22,bib,ab

L22  ANSWER 1 OF 1  WPIDS COPYRIGHT 2007       THE THOMSON CORP on STN
Full Text
AN   2000-475766 [41]   WPIDS
DNC  C2000-142626 [41]
TI   Use of adenosine agonists for cancer therapy
DC   B02
IN   COHN I; FISHMAN P
PA   (CANF-N) CAN-FITE BIOPHARMA LTD; (CANF-N) CAN-FITE TECHNOLOGIES LTD;
     (COHN-I) COHN I; (FISH-I) FISHMAN P
CYC  89
PIA  WO 2000040251   A1 20000713 (200041)* EN  37[2]
     AU 2000018884   A  20000724 (200052)  EN
     US 20010031742  A1 20011018 (200166)  EN
     EP 1140116      A1 20011010 (200167)  EN
     US 20020037871  A1 20020328 (200225)  EN
     JP 2002534390   W  20021015 (200282)  JA  43
     AU 757541       B  20030227 (200321)  EN
     US 6638914      B1 20031028 (200372)  EN
     US 6790839      B2 20040914 (200460)  EN
ADT  WO 2000040251 A1 WO 2000-IL14 20000107; AU 2000018884 A AU 2000-18884
     20000107; AU 757541 B AU 2000-18884 20000107; EP 1140116 A1 EP 2000-900112
     20000107; JP 2002534390 W JP 2000-592007 20000107; US 6790839 B2 CIP of US
     2000-700744 20000107; US 20010031742 A1 CIP of WO 2000-IL14 20000107; EP
     1140116 A1 WO 2000-IL14 20000107; US 20020037871 A1 CIP of WO 2000-IL14
     20000107; JP 2002534390 W WO 2000-IL14 20000107; US 6638914 B1 WO
     2000-IL14 20000107; US 6790839 B2 CIP of WO 2000-IL14 20000107; US
     20010031742 A1 CIP of US 2001-700744 20010109; US 20020037871 A1 CIP of US
     2001-700744 20010109; US 6638914 B1 US 2001-700744 20010109; US
     20010031742 A1 US 2001-782259 20010214; US 20020037871 A1 CIP of US
     2001-782259 20010214; US 6790839 B2 US 2001-782259 20010214; US
     20020037871 A1 US 2001-871963 20010604
FDT  AU 757541 B Previous Publ AU 2000018884 A; AU 2000018884 A Based on WO
     2000040251 A; EP 1140116 A1 Based on WO 2000040251 A; JP 2002534390 W
     Based on WO 2000040251 A; AU 757541 B Based on WO 2000040251 A; US 6638914
     B1 Based on WO 2000040251 A
PRAI IL 1999-127947 19990107
AB   WO 2000040251 A1   UPAB: 20060116
      NOVELTY - Use of an adenosine A1 receptor agonist (I) for the
     production of a composition for inducing proliferation of bone marrow
     cells.
           DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a
     treatment for patients undergoing cancer therapy which comprises (I) in
     combination with an anti-cancer chemotherapeutic drug or neuroleptic drug.
           ACTIVITY - Immunostimulant.
           MECHANISM OF ACTION - Adenosine A1 Receptor Agonist.
           Bone marrow cells were obtained from the femur of C57BL/6J mice.
     Cells were disaggregated by passing through a 25G needle. (3H)-Thymidine
     incorporation assay was used to evaluate the proliferative capability of
     the bone marrow cells.
           USE - (I) is useful for increasing the level of white blood cells
     in a cancer patient whose white blood cell count was reduced as a result
     of chemotherapy or radiotherapy. (I) may also be used to reduce risk of
     infection resulting from congenital or acquired neutropenias.
           ADVANTAGE - No advantage given.
           DESCRIPTION OF DRAWINGS - The drawing is a bar graph showing
     results of an in vitro assay in which proliferation of bone marrow cells
     was tested without adenosine (dense stripes) and with adenosine (spaced
     stripes) together with adenosine A1 receptor antagonist (DPCPX) and
     adenosine A2 receptor antagonist (DMPX) as compared to a control without
     any additional drug. The bar graph shows the results of a (3H)thymidine
     incorporation assay.


=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
```

```
                                                    ENTRY     SESSION
FULL ESTIMATED COST                                 65.84      359.84

FILE 'MEDLINE' ENTERED AT 08:28:06 ON 07 JAN 2007

 FILE LAST UPDATED: 6 Jan 2007 (20070106/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
  added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))
  and 2007 tree numbers.

  The annual reload will be available in early 2007.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s (A1 receptor? or A1 adenosine receptor?)
         22566 A1
        779544 RECEPTOR?
          2451 A1 RECEPTOR?
                 (A1(W)RECEPTOR?)
         22566 A1
        155447 ADENOSINE
        779544 RECEPTOR?
          1002 A1 ADENOSINE RECEPTOR?
                 (A1(W)ADENOSINE(W)RECEPTOR?)
L23       3096 (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)

=> s l23 and antagonist?
        542956 ANTAGONIST?
L24       2008 L23 AND ANTAGONIST?

=> s l24 and py<2002
      13447730 PY<2002
                 (PY<20020000)
L25       1592 L24 AND PY<2002

=> s l25 and (HIV or human immunodeficiency virus)
        166227 HIV
       1443662 HUMAN
        126045 IMMUNODEFICIENCY
        424555 VIRUS
         50103 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L26          0 L25 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l25 and (ADA or adenosine deaminase deficiency)
          5073 ADA
        155447 ADENOSINE
         11082 DEAMINASE
        226691 DEFICIENCY
           332 ADENOSINE DEAMINASE DEFICIENCY
                 (ADENOSINE(W)DEAMINASE(W)DEFICIENCY)
L27         17 L25 AND (ADA OR ADENOSINE DEAMINASE DEFICIENCY)

=> d l27,cbib,ab,1-17

L27  ANSWER 1 OF 17     MEDLINE on STN
2001156940.     PubMed ID: 11156949.   Leptin-induced lipolysis opposes the
     tonic inhibition of endogenous adenosine in white adipocytes. Fruhbeck G;
     Gomez-Ambrosi J; Salvador J. (Metabolic Research Laboratory, University of
     Navarra, and, Department of Endocrinology, Clinica Universitaria de
     Navarra, 31008-Pamplona, Spain.. gfruhbeck@unav.es) . The FASEB journal :
     official publication of the Federation of American Societies for
     Experimental Biology, (2001 Feb) Vol. 15, No. 2, pp. 333-40.  Journal
     code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language:
     English.
AB   The aim of the present study was to gain insight into the signaling
     pathway used by leptin to stimulate lipolysis.  The lipolytic rate of
     white adipocytes from sex- and age-matched lean (+/+) and fa/fa rats was
     determined in the absence or presence of leptin together with a number of
     agents acting at different levels of the signaling cascade.  Leptin did
     not modify FSK-, dbcAMP-, and IBMX-stimulated lipolysis.  Lipolysis can
     also be maximally stimulated by lowering media adenosine levels with
     adenosine deaminase (ADA), i.e., in the ligand-free state.  Although
```

ADA produced near maximal lipolysis in adipocytes of lean animals, only half of the maximal lipolytic rate (50.9+/-3.2%) was achieved in fat cells from fa/fa rats (P=0.0034). In adipocytes from lean animals preincubated with **ADA**, leptin caused a concentration-related stimulation of lipolysis (P=0.0001). However, leptin had no effect on the lipolytic activity of adipocytes in the ligand-free state from fa/fa rats. The adenosine **A1 receptor** agonist CPA effectively inhibited basal lipolysis in both lean and obese adipocytes (P=0.0001 and P=0.0090, respectively). Leptin had no effect on the lipolytic rate of adipocytes isolated from fa/fa rats and preincubated with CPA. When adipocytes were incubated with the **A1 receptor antagonist** DPCPX, a significant increase in glycerol release was observed in fa/fa fat cells (P=0.009), whereas cells isolated from lean rats showed no differences to **ADA**-stimulated lipolysis. After pretreatment with PTX, which inactivates receptor-mediated Gi function, adipocytes of obese rats became as responsive to the stimulatory actions of ISO as cells from lean rats (P=0.0090 vs. ISO in fa/fa rats; P=0.2416 vs. lean rats, respectively). PTX treatment of lean cells, however, did not alter their response to this lipolytic agent. It can be concluded that the lipolytic effect of leptin is located at the adenylate cyclase/Gi proteins level and that leptin-induced lipolysis opposes the tonic inhibition of endogenous adenosine in white adipocytes.

L27 ANSWER 2 OF 17 MEDLINE on STN

2000437742. PubMed ID: 10950874. Immunolocalization of **A1 adenosine receptors** in mammalian spermatozoa. Minelli A; Allegrucci C; Piomboni P; Mannucci R; Lluis C; Franco R. (Dipartimento di Medicina Sperimentale e Scienze Biochimiche, Sezione Biochimica Cellulare, Universita di Perugia, Perugia, Italia.. albami@tin.it) . The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society, **(2000 Sep)** Vol. 48, No. 9, pp. 1163-71. Journal code: 9815334. ISSN: 0022-1554. Pub. country: United States. Language: English.

AB The presence of **A1 adenosine receptors** (A1AR) in mammalian spermatozoa was previously demonstrated by radiochemical and immunochemical detection. This study was performed to investigate the cellular location of the A1AR to determine whether these receptors were somehow connected with ecto-adenosine deaminase and to evaluate their function in calcium uptake. By immunofluorescence staining we showed that in mammalian spermatozoa A1AR were constantly localized in the acrosomal region. This finding was confirmed by immunogold detection. Confocal analyses with anti-A1 and anti-**ADA** antibodies showed a high degree of co-localization. Calcium loading assay showed that this association was functional and affected calcium accumulation in mammalian spermatozoa. Therefore, we concluded that the acrosomal localization of A1AR was a constant feature in mammalian sperm. Moreover, these **A1 receptors** were functionally coupled to ecto-**ADA** and were able to modulate calcium uptake into an IP3-gated store.(J Histochem Cytochem 48:1163-1171, 2000)

L27 ANSWER 3 OF 17 MEDLINE on STN

2000140031. PubMed ID: 10676861. Adenosine modulation of D-[3H]aspartate release in cultured retina cells exposed to oxidative stress. Agostinho P; Caseiro P; Rego A C; Duarte E P; Cunha R A; Oliveira C R. (Center for Neurosciences of Coimbra, Faculty of Medicine, University of Coimbra, Portugal.) Neurochemistry international, **(2000 Mar)** Vol. 36, No. 3, pp. 255-65. Journal code: 8006959. ISSN: 0197-0186. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In this study we evaluated the role of adenosine receptor activation on the K+-evoked D-[3H]aspartate release in cultured chick retina cells exposed to oxidant conditions. Oxidative stress, induced by ascorbate (3.5 mM)/Fe2+ (100 microM), increased by about fourfold the release of D-[3H]aspartate, evoked by KCl 35 mM in the presence and in the absence of Ca2+. The agonist of **A1 adenosine receptors**, N6-cyclopentyladenosine (CPA; 10 nM), inhibited the K+-evoked D-[3H]aspartate release in control in oxidized cells. The **antagonist** of **A1 adenosine receptor**, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX; 50 nM), potentiated the release of D-[3H]aspartate in oxidized cells, and reverted the effect observed in the presence of CPA 10 nM. However, in oxidized cells, when DPCPX was tested together with CPA 100 nM the total release of D-[3H]aspartate increased from 5.1 +/- 0.4% to 11.4 +/- 1.0%, this increase being reverted by 3,7-dimethyl-1-propargylxanthine (DMPX; 100 nM), an **antagonist** of A2A adenosine receptors. In cells of both experimental conditions, the K+-evoked release of D-[3H]aspartate was potentiated by the selective agonist of A2A adenosine receptors, 2-[4-(2-carboxyethyl)phenethylamino]-5'-N-ethylcarboxamidoadenosin e (CGS 21680; 10 nM), whereas the **antagonist** of these receptors, DMPX (100 nM), inhibited the release of D-[3H]aspartate in oxidized cells, but not in

control cells. Adenosine deaminase (**ADA**; 1 U/ml), which is able to remove adenosine from the synaptic space, reduced the K+-evoked D-[3H]aspartate release, from 5.1 +/- 0.4% to 3.1 +/- 0.3% in oxidized cells, and had no significant effect in control cells. The extracellular accumulation of endogenous adenosine, upon K+-depolarization, was higher in oxidized cells than in control cells, and was reduced by the inhibitors of adenosine transporter (NBTI) and of ecto-5'-nucleotidase (AOPCP). This suggests that adenosine accumulation resulted from the outflow of adenosine mediated by the transporter, and from extracellular degradation of adenine nucleotide. Our data show that both inhibitory A1 and excitatory A2A adenosine receptors are present in cultured retina cells, and that the K+-evoked D-[3H]aspartate release is modulated by the balance between inhibitory and excitatory responses. Under oxidative stress conditions, the extracellular accumulation of endogenous adenosine seems to reach levels enough to potentiate the release of D-[3H]aspartate by the tonic activation of A2A adenosine receptors.

L27 ANSWER 4 OF 17 MEDLINE on STN

1999127771. PubMed ID: 9930581. Roles for adenosine A1- and A2-receptors in the control of thyrotrophin and prolactin release from the anterior pituitary gland. Kumari M; Buckingham J C; Poyser R H; Cover P O. (Department of Neuroendocrinology, Imperial College School of Medicine, Charing Cross Hospital, London, UK.) Regulatory peptides, **(1999 Jan 1)** Vol. 79, No. 1, pp. 41-6. Journal code: 8100479. ISSN: 0167-0115. Pub. country: Netherlands. Language: English.

AB Adenosine has been implicated in various aspects of pituitary function but little is known of its role in the regulation of thyrotrophin (TSH) release. This study examined the effects of adenosine deaminase (**ADA**, which provokes adenosine breakdown) and selective adenosine-receptor ligands on the secretion of immunoreactive (ir-) TSH and prolactin (PRL) by rat anterior pituitary segments in vitro. **ADA** (5 U/ml) stimulated the release of both hormones (P<0.01) as also did the selective adenosine **A1-receptor antagonist**, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, 0.1 & 1 nM, P<0.01); the responses to **ADA** were inhibited by an **A1-receptor** agonist, N6-cyclohexyladenosine (0.1-10 nM, P<0.01). A non-selective A1/A2-receptor agonist, N-cyclopropylcarboxamidoadenosine (1-100 nM) had mixed effects on ir-TSH release. However, the A2A-receptor selective agonist, CGS 21680 (1-100 nM) increased ir-TSH (P<0.05) and ir-PRL release (P<0.01); its effects on ir-TSH were blocked by concentrations of DPCPX (100 nM, P<0.01) sufficient to antagonize A2-receptors. These data suggest that adenosine acts via **A1-receptors** to tonically suppress ir-PRL and ir-TSH release but that A2A-receptor activation enhances the release of both hormones.

L27 ANSWER 5 OF 17 MEDLINE on STN

1999061674. PubMed ID: 9843917. Isolated superfused juxtaglomerular cells from rat kidney: a model for study of renin secretion. Albinus M; Finkbeiner E; Sosath B; Osswald H. (Department of Pharmacology, University of Tubingen, D-72074 T ubingen, Germany.) The American journal of physiology, **(1998 Dec)** Vol. 275, No. 6 Pt 2, pp. F991-7. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB Freshly isolated rat juxtaglomerular cells (JGC) were superfused to study renin secretion rate (RSR) at the cellular level. Effluates from the superfusion chamber collected in 20-min intervals showed a time-dependent decline in RSR from 85.5 +/- 32 to 4.0 +/- 2.4 ng ANG I. ml-1. h-1. mg protein-1. min-1 within 100 min of collection (mean +/- SE, n = no. of JGC preparations/superfusion chambers = 9/18). Addition of adenosine deaminase type II (**ADA** II, 3 U/1.4 mg protein) to the superfusion medium increased RSR more than fourfold to 402 +/- 100 ng in the first collection period, which dropped to 237.5 +/- 67 ng ANG I. ml-1. h-1. mg protein-1. min-1 (n = 9/18) within 100 min. This **ADA** II effect was rapid in onset and fully reversible. When the purified **ADA** type VII, with a 40-fold higher specific activity, was added to the superfusate, RSR was increased only by 96 +/- 17.8% compared with controls. This **ADA** VII (5 U/30 microgram) effect could be mimicked by the selective adenosine **A1-receptor antagonist** 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, 10(-6) mol/l). Since albumin stimulated RSR in a concentration-dependent fashion, to an extent similar to that of **ADA** II, we assume that the **ADA** II effect was largely unspecific in nature. We conclude that 1) superfusion of isolated JGC from rats is suitable for investigations of renin secretion at the cellular level, 2) the increase in RSR by **ADA** II appears to be only in part due to deamination of endogenously generated adenosine, and 3) albumin in the superfusate induces a similar stimulatory effect as **ADA** II.

L27 ANSWER 6 OF 17 MEDLINE on STN

97329833. PubMed ID: 9186292. Acute effects of progesterone on glucose metabolism in rat adipocytes: are they modulated by endogenous adenosine?. Sutter-Dub M T; Cordoba P. (Department of Endocrinology, University Bordeaux I, Talence, France.) Metabolism: clinical and experimental, **(1997 Jun)** Vol. 46, No. 6, pp. 595-604. Journal code: 0375267. ISSN: 0026-0495. Pub. country: United States. Language: English.

AB Progesterone rapidly inhibits glucose oxidation of isolated rat adipocytes. Because this inhibition is triggered by endogenous adenosine, the present study was designed to examine the effect of the steroid on cyclic adenosine monophosphate (cAMP) accumulation, its relation to lipolysis, and the possible participation of adenosine. The results strongly indicate that physiological concentrations of progesterone increase the release of adenosine by isolated adipocytes, with maximal release at the end of a 20-minute incubation. Progesterone decreased both cAMP levels and lipolysis in quiescent adipocytes or in adipocytes stimulated by isoproterenol. The increase of endogenous adenosine may explain the decline of cAMP and glycerol levels observed with progesterone. The effects of the steroid on lipolysis disappeared when adenosine was hydrolyzed by adenosine deaminase (**ADA**). On the other hand, in the absence of endogenous adenosine, the effect of progesterone on the cAMP level was decreased only in isoproterenol-stimulated cells. The inhibitory effects of progesterone on cAMP and glycerol production seem not to be related directly to the adenosine **A1 receptor**, for selective **A1 receptor antagonists** (8-cyclopentyl-1,3-dipropylxanthine [DPCPX] and CP 68,247) did not counteract these effects. However, mechanisms mediated by guanyl nucleotide binding proteins cannot be excluded. The decrease of cAMP and of lipolysis may be related to a stimulation of phosphodiesterases (PDEs). When PDEs I [Ca(2+)-calmodulin-regulated PDE family) were blocked by a selective inhibitor (CP 41,757), the progesterone inhibitory effect persisted, suggesting that PDEs I are not regulated by the steroid. On the other hand, the progesterone effect on cAMP accumulation but not on lipolysis disappeared in the presence of a selective inhibitor of the PDE IV family (cAMP-dependent-specific family). Ro 20.1724. When the specific inhibitor of PDE I or PDE IV was combined with **ADA**, the progesterone effect on cAMP disappeared. Taken together, these results suggest that the progesterone inhibitory action on cAMP levels was not mediated through **A1 receptors** or through activation of PDE I, but may be related to PDE IV activities. The progesterone effect on lipolysis seemed not to be directly related to changes in cAMP levels; an effect on PDE III activities in relation with the increase of adenosine release cannot be excluded.

L27 ANSWER 7 OF 17 MEDLINE on STN

97296914. PubMed ID: 9152383. Agonist-independent effect of an allosteric enhancer of the **A1 adenosine receptor** in CHO cells stably expressing the recombinant human **A1 receptor**. Kollias-Baker C A; Ruble J; Jacobson M; Harrison J K; Ozeck M; Shryock J C; Belardinelli L. (Department of Medicine, University of Florida, Gainesville, USA.) The Journal of pharmacology and experimental therapeutics, **(1997 May)** Vol. 281, No. 2, pp. 761-8. , Journal code: 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB The allosteric enhancer PD 81,723, a 2-amino-3-benzoylthiophene derivative, has been shown to potentiate agonist binding to **A1 adenosine receptors** (A1AdoRs) and to enhance the functional effects of adenosine and adenosine analogs. The objective of this study was to determine whether the apparent agonist-independent effect of PD 81,723 observed in CHO cells stably expressing the recombinant human A1AdoR was due to the potentiation of the action of endogenous adenosine, to the presence of constitutive receptor activity and/or to the binding of PD 81,723 to the agonist binding site of the A1AdoR. The allosteric enhancer PD 81,723, the A1AdoR agonist (R)-N6-(2-phenylisopropyl)adenosine and adenosine all significantly inhibited forskolin-stimulated cAMP accumulation in intact cells and increased [35S]-5'-(gamma-thio)triphosphate binding to cell membranes. The effects of adenosine on cAMP formation and [35S]-5'-(gamma-thio)triphosphate binding were attenuated by adenosine deaminase, but the effects of PD 81,723 were not. In the presence of **ADA**, the A1AdoR **antagonist** 8-cyclopentyl-1,3-dipropylxanthine increased forskolin-stimulated cAMP accumulation in cells expressing the recombinant human A1AdoR but not in nontransfected CHO cells. In binding experiments, the agonist (R)-N6-(2-phenylisopropyl)adenosine, but not PD 81,723, significantly displaced the specific binding of the A1AdoR agonist [3H]-N6-cyclohexyladenosine and the **antagonist** [3H]-8-cyclopentyl-1,3-dipropylxanthine. The results of this

study demonstrate that in CHO cells stably expressing the recombinant human A1AdoR, the agonist-independent effect of PD 81,723 is not due to potentiation of the action of endogenous adenosine or mediated by the binding of the allosteric enhancer to the agonist binding site of the recombinant human A1AdoR. It is possible that these effects are due to potentiation of constitutive receptor activity by PD 81,723.

L27 ANSWER 8 OF 17 MEDLINE on STN

97138904. PubMed ID: 8985888. Presynaptic A1 inhibitory/A2A facilitatory adenosine receptor activation balance depends on motor nerve stimulation paradigm at the rat hemidiaphragm. Correia-de-Sa P; Timoteo M A; Ribeiro J A. (Laboratory of Pharmacology, Instituto de Ciencias Biomedicas de Abel Salazar, University of Oporto, Portugal.) Journal of neurophysiology, **(1996 Dec)** Vol. 76, No. 6, pp. 3910-9. Journal code: 0375404. ISSN: 0022-3077. Pub. country: United States. Language: English.

AB 1. Adenosine modulates acetylcholine (ACh) release from the rat motor nerve terminals. Tonic activation of presynaptic A1 inhibitory and/or A2A facilitatory adenosine receptors is regulated by the concentration of the nucleoside at the synapse. The parameters (frequency, duration of pulses, train length) of nerve stimulation determine the amount of transmitter and/or modulator released, and have long been proposed as important features of synaptic control. This prompted us to investigate which was the prevailing response to adenosine on evoked [3H]-ACh release from rat phrenic nerve hemidiaphragm preparations in different stimulation conditions. 2. With low-frequency, short-duration pulses (5 Hz, 40 microseconds in duration), the adenosine inhibitory tonus (approximately 30%) predominates. The magnitude of the adenosine tonic inhibition was dependent on the number of pulses (250-750) delivered in each stimulation train, e.g., the facilitatory effect of adenosine deaminase (**ADA**, 0.5 U/ml) and the inhibitory effect of the adenosine uptake blocker S-(p-nitrobenzyl)-6-thioinosine (NBTI, 5 microM) reached significance only when > 250 pulses were applied. Facilitation was only observed with high concentrations of either exogenous adenosine (> 100 microM) or NBTI (> 10 microM). 3. When the stimulation pulse duration was increased to 1 ms (5 Hz, 750 pulses), endogenously generated adenosine consistently facilitated evoked [3H]-ACh release. In these conditions, **ADA** (0.5 U/ml) decreased evoked [3H]-ACh release by 29 +/- 4% (mean +/- SE) (n = 3), and both NBTI (3-30 microM) and adenosine (10-500 microM), which had biphasic effects with pulses of 40 microseconds, facilitated transmitter release. 4. When high-frequency "trains" (50 Hz, 40 microseconds, 500 pulses) were applied, both **ADA** (0.5 U/ml) and NBTI (5 microM) failed to modify evoked [3H]-ACh release. To bypass putative feedforward inhibition of ecto-5'-nucleotidase induced by released ATP, which might reduce adenosine formation during high-frequency trains, experiments containing a series of five high-frequency "bursts" (50 Hz, 40 microseconds, 100 pulses) with variable interburst intervals (5-20 s) were performed. In such conditions, the prevailing tonic response to adenosine turned out to be facilitatory, because **ADA** (0.5 U/ml) inhibited and NBTI (5 microM) facilitated evoked [3H]-ACh release. The magnitude of the inhibitory effect of **ADA** (0.5 U/ml) ranged from -9 +/- 6% (n = 4) to -54 +/- 8% (n = 5) as the interburst interval changed from 5 to 20 s, respectively. 5. Prolongation of individual pulses from 40 microseconds to 1 ms (5 Hz frequency) or increasing the frequency of stimulation (1-50 Hz, 40 microseconds) did not significantly change the excitatory effect of the A2A receptor agonist 2-[4-(2-p-carboxyethyl)phenylamino]-5'-N-ethylcarboxamidoadenosine (CGS 21680C). In contrast, the inhibitory effect of the **A1 receptor** agonist R-N6-phenylisopropyladenosine was significantly attenuated in both stimulation conditions. 6. In conclusion, the results suggest that high-intensity, high-frequency motor nerve stimulation critically influences endogenous adenosine formation and the A1/A2A receptor activation balance, i.e., it potentiates the tonic adenosine A2A-receptor-mediated facilitation of ACh release, whereas activation of the inhibitory **A1 receptors** becomes less effective. A model is proposed that attempts to further elucidate adenosine's involvement in synaptic transmission adaptation.

L27 ANSWER 9 OF 17 MEDLINE on STN

96134794. PubMed ID: 8594884. Adenosine inhibits arginine vasopressin-stimulated chloride secretion in a mouse IMCD cell line (mIMCD-K2). Moyer B D; McCoy D E; Lee B; Kizer N; Stanton B A. (Department of Physiology, Dartmouth Medical School, Hanover, New Hampshire 03755, USA.) The American journal of physiology, **(1995 Dec)** Vol. 269, No. 6 Pt. 2, pp. F884-91. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB Previously, we demonstrated that a mouse inner medullary collecting duct

cell line (mIMCD-K2) secretes Cl- by an electrogenic mechanism via cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channels [N. L. Kizer, B. Lewis, and B. A. Stanton. Am. J. Physiol. 268 (Renal Fluid Electrolyte Physiol. 37): F347-F355, 1995; N. L. Kizer, D. Vandorpe, B. Lewis, B. Bunting, J. Russell, and B. A. Stanton. Am. J. Physiol. 268 (Renal Fluid Electrolyte Physiol. 37): F854-F861, 1995; D. Vandorpe, N. Kizer, F. Ciampolillo-Bates, B. Moyer, K. Karlson, W. B. Guggino, and B. A. Stanton. Am. J. Physiol. 269 (Cell Physiol. 38): C683-C689, 1995]. The objective of the present study was to determine whether adenosine, and adenosine **A1 receptors** (A1AR) specifically, regulate electrogenic Cl- secretion (IscCl) in mIMCD-K2 cells. Neither N6-cyclohexyladenosine (CHA), a specific A1AR agonist, nor 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), a specific A1AR **antagonist**, altered basal, unstimulated IscCl in monolayers of mIMCD-K2 cells mounted in Ussing-type chambers. In contrast, DPCPX increased arginine vasopressin (AVP)-stimulated IscCl, an effect that was reversed by CHA. Adenosine deaminase (**ADA**), which oxidatively deaminates adenosine to inosine, increased AVP-stimulated IscCl. CHA reversed the stimulatory effect of **ADA** on AVP-stimulated IscCl. These results suggest that adenosine, via A1AR, inhibits AVP-stimulated IscCl. To identify the source(s) of extracellular adenosine, we examined the effects of dipyridamole, an inhibitor of nucleoside transport, and alpha,beta-methyleneadenosine 5'-diphosphate (AOPCP), an inhibitor of ecto-5'-nucleotidase, on AVP-stimulated IscCl. Both compounds increased AVP-stimulated IscCl. CHA reversed the stimulatory effect of dipyridamole and AOPCP on IscCl. Neither **ADA** nor CHA had an effect on 8-(4-chlorophenylthio)-adenosine 3',5'-cyclic monophosphate (CPT-cAMP)-stimulated IscCl. Moreover, U-73122, an inhibitor of phospholipase C, failed to attenuate the increase in AVP-stimulated IscCl elicited by dipyridamole and AOPCP or the decrease in AVP-stimulated IscCl elicited by CHA. We conclude that adenosine, released by a nucleoside transporter and formed extracellularly by the breakdown of AMP, binds to A1AR, and decreases AVP-stimulated IscCl in mIMCD-K2 cells by reducing intracellular cAMP levels.

L27 ANSWER 10 OF 17 MEDLINE on STN

94191831. PubMed ID: 8143055. Role of adenosine in the depolarization of hypoxic hamster diaphragm membrane in vitro. Esau S A. (Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville 22908.) American journal of respiratory and critical care medicine, **(1994 Apr)** Vol. 149, No. 4 Pt 1, pp. 910-4. Journal code: 9421642. ISSN: 1073-449X. Pub. country: United States. Language: English.

AB The resting membrane potential of in vitro hamster diaphragm muscle fibers is depolarized on exposure to hypoxia. It was hypothesized that this depolarization was mediated by adenosine. It was predicted that the treatment of well-oxygenated hamster diaphragm muscle strips in vitro with adenosine or adenosine agonists would depolarize the diaphragm fiber membrane. Furthermore, resting membrane potential of hypoxic diaphragm fibers would be repolarized by (1) the removal of adenosine by the enzyme adenosine deaminase (**ADA**), or (2) the addition of an adenosine **antagonist**, BW A1433. Adenosine (10(-4) M) depolarized the membrane by 8 +/- 1 mV ($p < 0.001$). The adenosine agonist cyclopentyladenosine, which has predominantly **A1 receptor** affinity, depolarized the membrane from -75.4 +/- 5.6 mV to -68.9 +/- 5.7 mV ($p < 0.001$). The A2 adenosine receptor agonist 5'-N-ethylcarboxamide adenosine did not cause a significant depolarization. The addition of **ADA** (2 unit/ml) to hypoxic muscle returned the resting membrane potential to that of well-oxygenated fibers, $p < 0.001$ versus hypoxia. BW A1433 (3 x 10(-7)) also restored the membrane potential of hypoxic muscle fibers from -72 +/- 1 mV to -79 +/- 1 mV ($p < 0.001$). These observations suggest that adenosine via the **A1 adenosine receptor** mediates the hypoxic depolarization of in vitro hamster diaphragm muscle. A direct effect of adenosine on muscle membrane has not been described previously.

L27 ANSWER 11 OF 17 MEDLINE on STN

94075613. PubMed ID: 8254024. The antiinflammatory mechanism of methotrexate. Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. Cronstein B N; Naime D; Ostad E. (Department of Medicine, New York University Medical Center, New York 10016.) The Journal of clinical investigation, **(1993 Dec)** Vol. 92, No. 6, pp. 2675-82. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Methotrexate, a folate **antagonist**, is a potent antiinflammatory agent when used weekly in low concentrations. We examined the hypothesis that the antiphlogistic effects of methotrexate result from its capacity to

promote intracellular accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) that, under conditions of cell injury, increases local adenosine release. We now present the first evidence to establish this mechanism of action in an in vivo model of inflammation, the murine air pouch model. Mice were injected intraperitoneally with either methotrexate or saline for 3-4 wk during induction of air pouches. Pharmacologically relevant doses of methotrexate increased splenocyte AICAR content, raised adenosine concentrations in exudates from carrageenan-inflamed air pouches, and markedly inhibited leukocyte accumulation in inflamed air pouches. The methotrexate-mediated reduction in leukocyte accumulation was partially reversed by injection of adenosine deaminase (**ADA**) into the air pouch, completely reversed by a specific adenosine A2 receptor **antagonist**, 3,7-dimethyl-1-propargylxanthine (DMPX), but not affected by an adenosine **A1 receptor antagonist**, 8-cyclopentyl-dipropylxanthine. Neither **ADA** nor DMPX affected leukocyte accumulation in the inflamed pouches of animals treated with either saline or the potent antiinflammatory steroid dexamethasone. These results indicate that methotrexate is a nonsteroidal antiinflammatory agent, the antiphlogistic action of which is due to increased adenosine release at inflamed sites.

L27 ANSWER 12 OF 17 MEDLINE on STN

94056804. PubMed ID: 8238380. Regulation of Na(+)-3HCO3- cotransport in rabbit proximal convoluted tubule via adenosine **A1 receptor**. Takeda M; Yoshitomi K; Imai M. (Department of Pharmacology, Jichi Medical School, Tochigi, Japan.) The American journal of physiology, **(1993 Oct)** Vol. 265, No. 4 Pt 2, pp. F511-9. Journal code: 0370511. ISSN: 0002-9513. Pub. country: United States. Language: English.

AB We investigated the role of adenosine **A1-receptor** in the regulation of basolateral Na(+)-3HCO3- cotransporter in the rabbit proximal convoluted tubule (PCT) microperfused in vitro by monitoring basolateral membrane potential and intracellular pH. FK-453, a highly specific A1 **antagonist**, inhibited basolateral HCO3- conductance in a concentration-dependent manner (10(-10)-10(-5) M). Other A1 **antagonists**, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) at 10(-5) M and theophylline at 10(-3) M, also had similar effects. N6-cyclohexyladenosine (CHA) at 10(-7) M attenuated the effect of low concentration (10(-8) M) of FK-453. Either enhancement of the degradation of adenosine by 0.1 U/ml adenosine deaminase (**ADA**) or inhibition of adenosine release from the cells by 10(-6) M S-(4-nitrobenzyl)-6-thioinosine (NBTI) mimicked the effects of A1 **antagonists**. These observations suggest that endogenous adenosine is released from PCT cells and stimulates Na(+)-3HCO3- cotransporter. Both 10(-4) M 8-(4-chlorophenylthio)-adenosine 3',5'-cyclic monophosphate (CPT-cAMP) and 10(-6) M forskolin also inhibited basolateral HCO3- conductance. Both 10(-6) M FK-453 and 10(-4) M CPT-cAMP decreased the initial rate as well as the magnitude of intracellular acidification induced by reduction of peritubular HCO3- concentration from 25 to 0 mM. Neither 10(-6) M FK-453 nor 10(-7) M CHA changed intracellular Ca2+ concentration as measured by fura-2 fluorescence. These results indicate that adenosine might stimulate HCO3- exit across the basolateral membrane through Na(+)-3HCO3- cotransporter by decreasing intracellular cAMP via **A1-receptor** activation.(ABSTRACT TRUNCATED AT 250 WORDS)

L27 ANSWER 13 OF 17 MEDLINE on STN

93226240. PubMed ID: 8469431. Facilitation of [3H]-ACh release by forskolin depends on A2-adenosine receptor activation. Correia-de-Sa P; Ribeiro J A. (Laboratory of Pharmacology, ICBAS, University of Oporto, Portugal.) Neuroscience letters, **(1993 Mar 5)** Vol. 151, No. 1, pp. 21-4. Journal code: 7600130. ISSN: 0304-3940. Pub. country: Netherlands. Language: English.

AB The effect of forskolin (FSK) on [3H]-acetylcholine release ([3H]-ACh) from the phrenic motor nerve terminals, and its modification by adenosine deaminase (**ADA**), by the A2-adenosine receptor agonist 2-[p-(2-carboxyethyl)phenethylamino]-5'-N-ethylcarboxamide adenosine (CGS 21680C), by the **A1-adenosine receptor** agonist R-N6-phenylisopropyl adenosine (R-PIA), by the A2-**antagonist** N-(2-(dimethylamino)-ethyl)-N-methyl-4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3 -dipropyl-1H-purine-8-yl)-benzene sulphonamide (PD 115,199), and by the A1-**antagonist** 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) were studied on the rat phrenic-hemidiaphragm preparation. It is concluded that the excitatory effect of FSK on evoked [3H]-ACh release depends on tonic A2-adenosine receptor activation.

L27 ANSWER 14 OF 17 MEDLINE on STN

93122469. PubMed ID: 8380395. Leukocyte adherence in rat mesenteric venules: effects of adenosine and methotrexate. Asako H; Wolf R E; Granger D N. (Department of Physiology, Center of Excellence for Arthritis and Rheumatology, Louisiana State University Medical Center, Shreveport.) Gastroenterology, **(1993 Jan)** Vol. 104, No. 1, pp. 31-7. Journal code: 0374630. ISSN: 0016-5085. Pub. country: United States. Language: English.

AB BACKGROUND: Methotrexate (MTX) reduces neutrophil adhesion to endothelial cell monolayers, possibly via stimulation of adenosine production. However, it remains unclear whether adenosine participates in the anti-inflammatory actions of MTX in postcapillary venules. METHODS: Leukocyte-endothelial cell adhesive interactions were measured in rat mesenteric venules (25-35 microns diameter) during superfusion with either bicarbonate-buffered saline (BBS) alone, BBS combined with platelet-activating factor (PAF), or BBS combined with leukotriene B4 (LTB4). In some experiments, either MTX or adenosine was added to a superfusate containing either PAF or LTB4. In other experiments, either adenosine deaminase (**ADA**), an adenosine **A1-receptor antagonist**, or an A2-receptor **antagonist** was added to a superfusate containing PAF and either MTX or adenosine. RESULTS: Both MTX and adenosine were effective in preventing the leukocyte-endothelial cell adhesive interactions elicited by PAF, but not by LTB4. These actions of adenosine and MTX against PAF-induced leukocyte adhesion were blunted by **ADA** and the A2-(but not the **A1-**) **receptor antagonist**. CONCLUSIONS: These results indicate that both adenosine and methotrexate attenuate PAF-induced leukocyte-endothelial cell adhesion in postcapillary venules via activation of A2-receptors on the leukocyte.

L27 ANSWER 15 OF 17 MEDLINE on STN

93108303. PubMed ID: 1469627. The role of adenosine in glycine-induced glomerular hyperfiltration in rats. Wang Y X; Brooks D P. (Department of Renal Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania.) The Journal of pharmacology and experimental therapeutics, **(1992 Dec)** Vol. 263, No. 3, pp. 1188-94. Journal code: 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB Ingestion of a high-protein diet or infusion of amino acids induces glomerular hyperfiltration and hyperemia. We have investigated the role of endogenous adenosine in glycine-induced hyperfiltration. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured in conscious chronically instrumented rats. Glycine (3.7 mg/min, i.v.; n = 6) significantly increased GFR and ERPF from 0.92 +/- 0.07 to 1.13 +/- 0.08 and 3.28 +/- 0.24 to 3.69 +/- 0.19 ml/min.100 g, respectively. In the presence of adenosine deaminase (**ADA**, 2 U/kg.min, n = 6), glycine-induced glomerular hyperfiltration and hyperemia were blunted. The small changes in GFR (from 0.86 +/- 0.06 to 0.90 +/- 0.10 ml/min.100 g) and ERPF (from 3.60 +/- 0.57 to 3.83 +/- 0.53 ml/min x 100 g) were not statistically significant. Erythro-9-(2-hydroxy-3-nonyl) adenosine hydrochloride (100 micrograms/kg.min, n = 6), an **ADA** inhibitor, reversed the effect of **ADA**. Injection of 8-phenyltheophylline (10 mg/kg, n = 6), an adenosine **A1 receptor antagonist** that alone did not affect GFR, abolished the glycine-induced glomerular hyperfiltration (GFR from 1.02 +/- 0.08 to 0.93 +/- 0.08 ml/min.100 g, P > .05). 8-phenyltheophylline, which itself decreased ERPF, also significantly decreased the ERPF response to glycine (3.47 +/- 0.26 to 2.78 +/- 0.14 ml/min x 100 g). Thus, endogenous adenosine, acting at adenosine **A1 receptors**, plays an important role in the glomerular hyperfiltration and hyperemia induced by glycine.

L27 ANSWER 16 OF 17 MEDLINE on STN

92148453. PubMed ID: 1738001. Magnesium-dependent enhancement of endogenous agonist binding to **A1 adenosine receptors**: a complicating factor in quantitative autoradiography. Parkinson F E; Fredholm B B. (Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden.) Journal of neurochemistry, **(1992 Mar)** Vol. 58, No. 3, pp. 941-50. Journal code: 2985190R. ISSN: 0022-3042. Pub. country: United States. Language: English.

AB Quantitative autoradiography was used to investigate the effects of Mg2+ on agonist and **antagonist** binding to **A1 receptors** in rat striatum. **A1 receptors** were labelled with the selective agonist N6-[3H]cyclohexyladenosine ([3H]CHA) or the selective **antagonist** 1,3-[3H]dipropyl-8-cyclopentylxanthine ([3H]DPCPX). Mg2+ had no significant effect on equilibrium binding constants for [3H]CHA [control: KD (95% confidence interval) of 0.34 (0.15-0.80) nM and Bmax of 267 +/- 8 fmol/mg of gray matter; with 10 mM Mg2+: KD of 0.8 (0.13-4.9) nM and Bmax of 313 +/- 8.9 fmol/mg of gray matter] or [3H]DPCPX [control: KD of 0.54 (0.30-0.99) nM and Bmax of 256 +/- 2.3 fmol/mg of gray matter; with 10 mM

Mg2+: KD of 1.54 (0.2-11.0) nM and Bmax of 269 +/- 35.7 fmol/mg of gray matter]. In contrast, Mg2+ slowed the apparent association rate for both ligands; this was observed as a shift from a one-component to a two-component model for [3H]DPCPX. Mg2+ also affected the dissociation rates of both ligands; for [3H]CHA, dissociation in the presence of Mg2+ was not detected. Mg2+ produced a concentration-dependent inhibition of [3H]CHA binding only prior to equilibrium. HPLC was performed on untreated sections, sections preincubated with adenosine deaminase (**ADA**), and sections preincubated with **ADA** and incubated with **ADA** in the absence or presence of Mg2+. Adenosine was found in measurable quantities under all conditions, and the concentration was not influenced by Mg2+ or by the inclusion of GTP in the preincubation medium. From these data, we conclude the following: (a) adenosine is present and may be produced continuously in brain sections; (b) **ADA** is not capable of completely eliminating the produced adenosine; (c) Mg2+ apparently does not influence adenosine production or elimination; (d) **A1 receptor**-guanine nucleotide binding protein coupling is maximal in this preparation; and (e) Mg2+ decreases the dissociation rate of bound endogenous adenosine from **A1 receptors**, thus limiting the access of [3H]CHA and [3H]DPCPX to the receptors. Thus, enhancement of endogenous adenosine binding to **A1 receptors** by Mg2+ is a complicating factor in receptor autoradiography and may be so in other preparations as well.

L27 ANSWER 17 OF 17 MEDLINE on STN
83232291. PubMed ID: 6305455. Inhibition of brain adenylate cyclase by **A1 adenosine receptors**: pharmacological characteristics and locations. Ebersolt C; Premont J; Prochiantz A; Perez M; Bockaert J. Brain research, **(1983 May 9)** Vol. 267, No. 1, pp. 123-9. Journal code: 0045503. ISSN: 0006-8993. Pub. country: Netherlands. Language: English.
AB When tested under conditions reducing the endogenous production of adenosine (presence of adenosine deaminase (**ADA**) 1.6 IU/ml; and deoxyadenosine triphosphate (d-ATP), and in the presence of both NaCl and GTP, the **ADA**-resistant analog phenylisopropyladenosine (PIA) inhibited the adenylate cyclase of several brain tissues. These tissues included: (1) 5 brain areas of adult rats (frontal and parietal cortex, cerebellum cortex, hippocampus and striatum)--hypothalamus and mid-brain adenylate cyclases were not inhibited by PIA; (2) astrocytes in primary cultures prepared from cerebral cortex of newborn mice; and (3) neurons in primary cultures prepared from striata of 15-day-old mouse embryos. The specificity profile of the adenosine receptor involved in the inhibition was determined in astrocytes. It was typical of an **A1 adenosine receptor** (high affinity of PIA; Ka app: 9 +/- 5 X 10(-9) M (n = 4) compared to the affinity of 5'-N-ethylcarboxamide adenosine (NECA); Ka app: 1.3 +/- 0.6 X 10(-7) M (n = 3). There was an excellent correlation between the affinities of several adenosine agonists and **antagonists** for **A1 receptors** coupled with an adenylate cyclase in astrocytes and for the receptors labeled with N6-cyclohexyl-[3H]adenosine in brain cortex. In adult rat striatum as well as in astrocytes and striatal neurons in culture the adenylate cyclase was inhibited by low PIA concentrations through **A1 receptors** and stimulated by higher concentrations through A2 receptors. In contrast, A2 receptors were not detected in adult rat cerebral cortex. In adult rat striatum, A1 and dopamine receptors coupled with an adenylate cyclase seemed to be located on different cell populations. In contrast, in astrocytes A1 and beta-adrenergic receptors coupled with adenylate cyclase were apparently located on the same cells.

=> d his

(FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
E WILSON CONSTANCE N/IN
L1 3 S E4

FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
E WILSON C N/IN
L2 19 S E3
L3 8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
E WILSON C N/AU
L4 96 S E3
L5 1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

```
     FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6          2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7          1803 S L6 AND ANTAGONIST?
L8           319 S L7 AND (ADENOSINE.RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9           140 S L8 AND ANTAGONIST?/CLM
L10           61 S L9 AND AY<2002
L11            4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12           57 S L10 NOT L11
L13            1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14           56 S L10 NOT (L11 OR L13)
L15           10 S L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)
L16            1 F FILE WPIDS

     FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
L17          214 S (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)
L18          123 S L17 AND ANTAGONIST?
L19           62 S L18 AND PY<2002
L20            0 S L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOS
L21            2 S L19 AND (IMMUNOLOG?)
L22            1 S L19 AND (INFECT?)

     FILE 'MEDLINE' ENTERED AT 08:28:06 ON 07 JAN 2007
L23         3096 S (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)
L24         2008 S L23 AND ANTAGONIST?
L25         1592 S L24 AND PY<2002
L26            0 S L25 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L27           17 S L25 AND (ADA OR ADENOSINE DEAMINASE DEFICIENCY)

=> s l25 and review?
        677887 REVIEW?
L28            8 L25 AND REVIEW?

=> d l28,cbib,ab,1-8

L28  ANSWER 1 OF 8      MEDLINE on STN
2001070093.     PubMed ID: 11126837.   Role of adenosine in contrast
     media-induced acute renal failure in diabetes mellitus. Pflueger A; Larson
     T S; Nath K A; King B F; Gross J M; Knox F G. (Department of Physiology
     and Biophysics, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA. )
     Mayo Clinic proceedings. Mayo Clinic, (2000 Dec) Vol. 75, No. 12, pp.
     1275-83.  Ref: 77. Journal code: 0405543. ISSN: 0025-6196. Pub. country:
     United States. Language: English.
AB   Increased release of renal adenosine and stimulation of renal adenosine
     receptors have been proposed to be major mechanisms in the development of
     contrast media-induced acute renal failure (CM-ARF). Patients with
     diabetes mellitus or preexisting renal disease who have reduced renal
     function have a markedly increased risk to develop CM-ARF. This increased
     risk to develop CM-ARF in patients with diabetes mellitus is linked to a
     higher sensitivity of the renal vasculature to adenosine, since
     experimental studies have shown increased adenosine-induced
     vasoconstriction in the kidneys of diabetic animals. Furthermore, recent
     evidence suggests that administration of adenosine receptor antagonists
     reduces the risk of development of CM-ARF in both diabetic and nondiabetic
     patients. The purpose of this review is to discuss the role of
     adenosine in the development of CM-ARF, particularly in the kidneys of
     diabetic patients, and to evaluate the therapeutic potential of adenosine
     receptor antagonists in the prevention of CM-ARF. Selective adenosine
     A1 receptor antagonists may provide a therapeutic tool to prevent
     CM-ARF in patients with diabetes mellitus and reduced renal function.

L28  ANSWER 2 OF 8      MEDLINE on STN
2000491971.     PubMed ID: 11000420.   Adenosinergic modulation of basal
     forebrain and preoptic/anterior hypothalamic neuronal activity in the
     control of behavioral state. Strecker R E; Morairty S; Thakkar M M;
     Porkka-Heiskanen T; Basheer R; Dauphin L J; Rainnie D G; Portas C M;
     Greene R W; McCarley R W. (Department of Psychiatry, VA Medical Center and
     Harvard Medical School, Psychiatry, 116A, 940 Belmont St., Brockton, MA
     02301, USA.. robert_mccarley@hms.harvard.edu) . Behavioural brain
     research, (2000 Nov) Vol. 115, No. 2, pp. 183-204. Journal code:
     8004872. ISSN: 0166-4328. Pub. country: Netherlands. Language: English.
AB   This review describes a series of animal experiments that investigate
     the role of endogenous adenosine (AD) in sleep. We propose that AD is a
     modulator of the sleepiness associated with prolonged wakefulness. More
     specifically, we suggest that, during prolonged wakefulness, extracellular
     AD accumulates selectively in the basal forebrain (BF) and cortex and
```

promotes the transition from wakefulness to slow wave sleep (SWS) by inhibiting cholinergic and non-cholinergic wakefulness-promoting BF neurons at the AD **A1 receptor**. New in vitro data are also compatible with the hypothesis that, via presynaptic inhibition of GABAergic inhibitory input, AD may disinhibit neurons in the preoptic/anterior hypothalamus (POAH) that have SWS-selective activity and Fos expression. Our in vitro recordings initially showed that endogenous AD suppressed the discharge activity of neurons in the BF cholinergic zone via the AD-**A1 receptor**. Moreover, in identified mesopontine cholinergic neurons, AD was shown to act post-synaptically by hyperpolarizng the membrane via an inwardly rectifying potassium current and inhibition of the hyperpolarization-activated current, I(h). In vivo microdialysis in the cat has shown that AD in the BF cholinergic zone accumulates during prolonged wakefulness, and declines slowly during subsequent sleep, findings confirmed in the rat. Moreover, increasing BF AD concentrations to approximately the level as during sleep deprivation by a nucleoside transport blocker mimicked the effect of sleep deprivation on both the EEG power spectrum and behavioral state distribution: wakefulness was decreased, and there were increases in SWS and REM sleep. As predicted, microdialyis application of the specific **A1 receptor antagonist** cyclopentyltheophylline (CPT) in the BF produced the opposite effects on behavioral state, increasing wakefulness and decreasing SWS and REM. Combined unit recording and microdialysis studies have shown neurons selectively active in wakefulness, compared with SWS, have discharge activity suppressed by both AD and the A1-specific agonist cyclohexyladenosine (CHA), while discharge activity is increased by the **A1 receptor antagonist**, CPT. We next addressed the question of whether AD exerts its effects locally or globally. Adenosine accumulation during prolonged wakefulness occurred in the BF and neocortex, although, unlike in the BF, cortical AD levels declined in the 6th h of sleep deprivation and declined further during subsequent recovery sleep. Somewhat to our surprise, AD concentrations did not increase during prolonged wakefulness (6 h) even in regions important in behavioral state control, such as the POAH, dorsal raphe nucleus, and pedunculopontine tegmental nucleus, nor did it increase in the ventrolateral/ventroanterior thalamic nucleii. These data suggest the presence of brain region-specific differences in AD transporters and/or degradation that become evident with prolonged wakefulness, even though AD concentrations are higher in all brain sites sampled during the naturally occurring (and shorter duration) episodes of wakefulness as compared to sleep episodes in the freely moving and behaving cat. Might AD also produce modulation of activity of neurons that have sleep selective transcriptional (Fos) and discharge activity in the preoptic/anterior hypothalamus zone? Whole cell patch clamp recordings in the in vitro horizontal slice showed fast and likely GABAergic inhibitory post-synaptic potentials and currents that were greatly decreased by bath application of AD. Adenosine may thus disinhibit and promote expression of sleep-related neuronal activity in the POAH. In summary, a growing body of evidence supports the role of AD as a mediator of the sleepiness following prolonged wakefulness, a role in which its inhibitory actions on the BF wakefulness-promoting neurons may be especially important.

L28 ANSWER 3 OF 8 MEDLINE on STN

2000013124. PubMed ID: 10545129. The action is at the terminal. Pittman Q J. (Neuroscience Research Group, Department of Physiology and Biophysics, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1.) The Journal of physiology, **(1999 Nov 1)** Vol. 520 Pt 3, pp. 629. Ref: 7. Journal code: 0266262. ISSN: 0022-3751. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The magnocellular neurons of the supraoptic nucleus have been intensively studied because of their unique bursting and phasic activity patterns. While these can be explained in part by intrinsic membrane conductances, it is now also apparent that afferent inputs are important in sculpting and initiating the activity patterns. Modulation of these inputs, therefore, provides a powerful way to regulate magnocellular neuronal activity. The paper by Oliet & Poulain in this issue of The Journal of Physiology provides evidence that adenosine may be such a modulator in that it acts presynaptically in the supraoptic nucleus (SON) to inhibit both excitatory and inhibitory synaptic currents onto magnocellular neurons. Furthermore, the authors were able to demonstrate an action of endogenous adenosine in the slice by blocking, with an A1-type **antagonist**, a progressive synaptic depression brought about by continuous afferent stimulation at 1 Hz over 2 min or more. This paper therefore adds to a compelling body of evidence that adenosine has transmitter action in the central nervous system (Dunwiddie, 1985).

Several aspects of this study deserve comment and raise questions amenable to experimentation. Adenosine was equipotent in inhibiting IPSCs and EPSCs, thereby raising questions as to the consequences of adenosine action on the output of the nucleus. While it could be argued that intense excitatory inputs would be attenuated, the same would be true for inhibition, making the net effect rather minor. One possible effect could be to stabilize activity levels of the postsynaptic cell at levels conducive for the generation of intrinsic voltage-dependent activity patterns. Another possibility is that adenosine is simply acting to reduce overall metabolic activity; since the metabolic consequences of activity in the presynaptic terminal would be similar in excitatory and inhibitory terminals, it may be irrelevant as to the nature of the transmitter. It is also interesting that the maximum inhibition attained in response to adenosine is only 60 % for either excitatory or inhibitory inputs. This is in contrast to such presynaptic modulators as baclofen, acting at GABAB receptors, where there is 100 % attenuation of afferent evoked potentials (Pittman et al. 1998). Whether this is due to a distribution of adenosine receptors on only a limited number of afferent terminals, or whether it reflects a mechanism of action that is only partially effective in reducing the transmitter release is not known. For example, if adenosine receptors were coupled to only a subset of the calcium channels engaged in transmitter release, one might predict that only part of the transmitter release would be inhibited. However, data from the Oliet & Poulain paper indicate that miniature EPSCs and miniature IPSCs are inhibited by adenosine; as most evidence indicates that TTX-resistant spontaneous currents in magnocellular neurons are calcium insensitive, this suggests that adenosine acts downstream of the calcium influx, perhaps by interfering with the transmitter release machinery (**reviewed** in Wu & Saggau, 1997). It would also be interesting to determine whether the presynaptic **A1 receptors** identified here display a sensitivity to pertussis toxin pretreatment. While such receptors are known to be G-protein coupled, presynaptic receptors are often insensitive to inhibition by pertussis toxin. The identification of an action of endogenous adenosine required repetitive stimulation, perhaps because reuptake mechanisms at lower frequencies efficiently removed adenosine. The source of this endogenous adenosine is still unknown. While it could be released by a nucleoside transporter from either glial cells or neurons, another possibility is that it may be produced by metabolic breakdown of ATP (Cunha et al. 1998). ATP is known to be released in the SON from noradrenergic afferents (Buller et al. 1996) and there is also some evidence that it may be released from the magnocellu

L28 ANSWER 4 OF 8 MEDLINE on STN

1999198283. PubMed ID: 10098210. Paracrine regulation of renal hemodynamics. Aki Y; Abe Y; Tamaki T. (Department of Pharmacology, Kagawa Medical School, Japan.) Nippon yakurigaku zasshi. Folia pharmacologica Japonica, **(1998 Nov)** Vol. 112, No. 5, pp. 287-98. Ref: 36. Journal code: 0420550. ISSN: 0015-5691. Pub. country: Japan. Language: Japanese.

AB There has been an intense interest in multiple interacting paracrine systems that influence renal hemodynamics. The contractile responses at different sites along the renal vascular network exhibit distinct characteristics, depending on their receptor populations or activation mechanisms. These differences in effector mechanisms have also coupled with variations in paracrine signals from adjoining endothelial and epithelial cells. In this **review**, we have focused on the roles of nitric oxide (NO) and adenosine in the regulation of renal microvasculature and how they interact with other vasoactive factors. Vasopressin (VP) V2 receptors as well as V1 receptors exist in renal vasculature, especially in afferent arterioles, and V2-receptor stimulation induced vasodilation. V2-receptor-mediated vasodilation was attenuated by L-NNA. In addition, Ang II did not affect the diameter of isolated rabbit afferent arterioles, but after the treatment of L-NNA, Ang II exerted a dose-dependent vasoconstriction. Thus, NO modulated the renal vascular actions of VP and Ang II. Adenosine causes vasoconstriction via the **A1 receptors**, which are restricted primarily to the afferent arterioles. This selective action of adenosine suggests that adenosine exerts selective control of the renal vasculature. Adenosine augmented renal vasoconstriction by NE and Ang II via the adenosine **A1 receptor**, and the **A1 receptor antagonist** significantly reduced NE- or Ang II-induced renal vasoconstriction. The plurality of these interactions indicates that while it is very important to understand the specific direct cellular actions of each individual factor, it is equally important to understand how the various interactions are orchestrated under in vivo conditions.

L28 ANSWER 5 OF 8 MEDLINE on STN

96015204. PubMed ID: 7579840. The role of ATP sensitive potassium channels in myocardial protection. Cason B A; Gordon H J; Avery E G 4th; Hickey R F. (Department of Anesthesia, University of California, San Francisco, USA.) Journal of cardiac surgery, **(1995 Jul)** Vol. 10, No. 4 Suppl, pp. 441-4. Ref: 32. Journal code: 8908809. ISSN: 0886-0440. Pub. country: United States. Language: English.

AB Several factors have pointed to a potential link between ATP sensitive potassium channel activation in ventricular myocytes and the phenomenon of myocardial preconditioning. Preconditioning can be blocked by adenosine **antagonists**, and is mimicked by adenosine **A1-receptor** agonists. A portion of the physiological action of adenosine is, however attributable to adenosine actions on KATP channels. The adenosine **A1 receptor** is reported to be linked to the KATP channel in rat ventricular myocytes by a G-protein mechanism. This article will **review** the current status of work regarding the role of KATP channels in myocardial preconditioning and will highlight recent work addressing the role of anesthetic effects in these studies. Recent reports and work from our laboratory reveal that several commonly used anesthetic drugs either have direct effects on KATP channels (barbiturates) or have prominent physiological effects that are modulated in large part by KATP channels (volatile anesthetics halothane and isoflurane).

L28 ANSWER 6 OF 8 MEDLINE on STN

94275913. PubMed ID: 8007033. Adenosine receptors are not involved in theophylline-induced seizures. Hornfeldt C S; Larson A A. (University of Minnesota, St. Paul, Minnesota.) Journal of toxicology. Clinical toxicology, **(1994)** Vol. 32, No. 3, pp. 257-65. Journal code: 8213460. ISSN: 0731-3810. Pub. country: United States. Language: English.

AB One of the most dangerous aspects of theophylline toxicity is seizures. A **review** of the literature suggests that current anticonvulsant therapy remains far from optimal. As it is known that some of the pharmacologic effects of theophylline occur via antagonism of the adenosine **A1 receptor**, we tested the hypothesis that agonists acting at the adenosine **A1 receptor** can inhibit seizures caused by toxic doses of theophylline in mice. Dose-response curves were constructed for the ability of theophylline to produce tonic seizures in animals pre-treated with vehicle or several adenosine **A1 receptor** agonists. The LD50 (95% CI) for each dose-response curve was calculated. The results of these experiments showed that pretreatment with the direct-acting adenosine A1 agonists carbamazepine and cyclohexyladenosine and the indirect-acting agonist dipyridamole each failed to inhibit the ability of theophylline to cause tonic seizures ($p > 0.05$). Failure of these drugs to protect against theophylline-induced seizures suggests these seizures are produced by other mechanisms. Based on our results, adenosine A1 agonists, such as carbamazepine, appear to offer no therapeutic benefit in the treatment of theophylline-induced seizures.

L28 ANSWER 7 OF 8 MEDLINE on STN

94153758. PubMed ID: 8110616. Mechanisms of pain in angina pectoris--a critical **review** of the adenosine hypothesis. Sylven C. (Karolinska Institute, Department of Medicine, Huddinge University Hospital, Sweden.) Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy, **(1993 Nov)** Vol. 7, No. 5, pp. 745-59. Ref: 141. Journal code: 8712220. ISSN: 0920-3206. Pub. country: United States. Language: English.

AB Clinical characteristics: Angina pectoris represents a visceral pain caused by reversible myocardial ischemia. The majority of ischemic attacks are symptomless. When pain is manifested, it appears late during the ischemic event. The pain is complex in its quality and bears little relation to the region of myocardial ischemia. Pain shows a sensitive dependence on initial conditions suggesting a mechanism with deterministic chaotic dynamics for the association between myocardial ischemia and pain. Neurophysiological substrate: Ganglia are present within the heart, particularly in epicardial fat. The blood supply of intrinsic cardiac ganglia arises primarily from branches of the proximal coronary arteries. Both afferent and efferent neurons within the intrinsic cardiac nervous system exist, while the majority of neurons in that location may be local circuit neurons. Integration takes place not only in the intrinsic cardiac nervous system, but also in mediastinal, middle cervical, and stellate ganglia. Cardiac afferent receptors are also connected to cell bodies in dorsal root and nodose ganglia, as well as intrathoracic ganglia. Myocardial regions have no spatial representation in these ganglia. Adenosine, among a number of substances, can modulate the activity generated by cardiac afferent nerve endings and intrinsic cardiac

neurons. Such effects appear to be exerted at **A1 receptors**. Adenosine as a pain messenger: During myocardial ischemia adenosine is released in large quantities into the interstitial space. The endothelium takes up the major amount of adenosine. Thus only small increments of adenosine are detected in the blood-stream. Given as an intravenous bolus to healthy volunteers or to patients with ischemic heart disease and angina pectoris, adenosine provokes angina pectorislike pain, which is similar to habitual angina pectoris with regard to quality and location. Pain is provoked in the absence of ECG signs of ischemia. Patients with asymptomatic myocardial ischemia are less sensitive to adenosine, whereas patients with Syndrome X are more sensitive with respect to adenosine-provoked pain. When adenosine is given intraarterially, including into the coronary arteries, pain is provoked in the corresponding vascular bed. Adenosine-provoked pain and ischemic pain are counteracted by previous administration of the adenosine receptor **antagonist** theophylline.(ABSTRACT TRUNCATED AT 400 WORDS)

L28 ANSWER 8 OF 8 MEDLINE on STN
84142617. PubMed ID: 6199685. Adenosine receptor interactions and anxiolytics. Bruns R F; Katims J J; Annau Z; Snyder S H; Daly J W. Neuropharmacology, **(1983 Dec)** Vol. 22, No. 12B, pp. 1523-9. Ref: 28. Journal code: 0236217. ISSN: 0028-3908. Pub. country: ENGLAND: United Kingdom. Language: English.
AB [3H]-N6-cyclohexyladenosine and [3H]-1,3-diethyl-8-phenylxanthine label the A1 subtype of adenosine receptor in brain membranes. The affinities of methylxanthines in competing for **A1 adenosine receptors** parallel their potencies as locomotor stimulants. The adenosine agonist N6-(phenylisopropyl) adenosine is a potent locomotor depressant. Both diazepam and N6-(L-phenylisopropyl)adenosine cause locomotor stimulation in a narrow range of subdepressant doses. Combined stimulant doses of the two agents depress motor activity, as do larger doses of either one, given separately. Evidence supporting and against the hypothesis that some of the actions of benzodiazepines are mediated via the adenosine system is **reviewed**. A number of compounds interact with both systems, probably because of physico-chemical similarities between adenosine and diazepam. It is concluded that of the four classic actions of benzodiazepines, the sedative and muscle relaxant (but not anxiolytic or anticonvulsant) actions could possibly be mediated by adenosine.

=> d his

(FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
E WILSON CONSTANCE N/IN
L1 3 S E4

FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
E WILSON C N/IN
L2 19 S E3
L3 8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
E WILSON C N/AU
L4 96 S E3
L5 1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6 2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7 1803 S L6 AND ANTAGONIST?
L8 319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9 140 S L8 AND ANTAGONIST?/CLM
L10 61 S L9 AND AY<2002
L11 4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12 57 S L10 NOT L11
L13 1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14 56 S L10 NOT (L11 OR L13)
L15 10 S L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)
L16 1 F FILE WPIDS

FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
L17 214 S (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)
L18 123 S L17 AND ANTAGONIST?
L19 62 S L18 AND PY<2002

```
L20           0 S L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOS
L21           2 S L19 AND (IMMUNOLOG?)
L22           1 S L19 AND (INFECT?)

     FILE 'MEDLINE' ENTERED AT 08:28:06 ON 07 JAN 2007
L23        3096 S (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)
L24        2008 S L23 AND ANTAGONIST?
L25        1592 S L24 AND PY<2002
L26           0 S L25 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L27          17 S L25 AND (ADA OR ADENOSINE DEAMINASE DEFICIENCY)
L28           8 S L25 AND REVIEW?

=> s (P2x receptor? or P2-purinoceptor?)
          1982 P2X
        779544 RECEPTOR?
           933 P2X RECEPTOR?
                 (P2X(W)RECEPTOR?)
         20630 P2
          3726 PURINOCEPTOR?
           771 P2-PURINOCEPTOR?
                 (P2(W)PURINOCEPTOR?)
L29        1655 (P2X RECEPTOR? OR P2-PURINOCEPTOR?)

=> s l29 and antagonist?
        542956 ANTAGONIST?
L30        892 L29 AND ANTAGONIST?

=> s l30 and (HIV or human immunodeficiency virus or adenosine deaminase deficiency)
        166227 HIV
       1443662 HUMAN
        126045 IMMUNODEFICIENCY
        424555 VIRUS
         50103 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
        155447 ADENOSINE
         11082 DEAMINASE
        226691 DEFICIENCY
           332 ADENOSINE DEAMINASE DEFICIENCY
                 (ADENOSINE(W)DEAMINASE(W)DEFICIENCY)
L31           0 L30 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADENOSINE DEAMIN
                ASE DEFICIENCY)

=> s (HIV or human immunodeficiency virus)
        166227 HIV
       1443662 HUMAN
        126045 IMMUNODEFICIENCY
        424555 VIRUS
         50103 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L32     171687 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l32 and (adenosine receptor? or purinoceptor?)
        155447 ADENOSINE
        779544 RECEPTOR?
          5520 ADENOSINE RECEPTOR?
                 (ADENOSINE(W)RECEPTOR?)
          3726 PURINOCEPTOR?
L33          5 L32 AND (ADENOSINE RECEPTOR? OR PURINOCEPTOR?)

=> d 133,cbib,ab,1-5

L33  ANSWER 1 OF 5     MEDLINE on STN
2006374564.     PubMed ID: 16522819.   Adenosine A2a receptors induce
     heterologous desensitization of chemokine receptors. Zhang Ning; Yang De;
     Dong Huifang; Chen Qian; Dimitrova Dessislava I; Rogers Thomas J;
     Sitkovsky Michail; Oppenheim Joost J. (Laboratory of Molecular
     Immunoregulation, Center for Cancer Research and Basic Research Program,
     Science Applications International-Frederick, National Cancer Institute at
     Frederick, Frederick, MD 21702, USA. ) Blood, (2006 Jul 1) Vol. 108, No.
     1, pp. 38-44.  Electronic Publication: 2006-03-07. Journal code: 7603509.
     ISSN: 0006-4971. Pub. country: United States. Language: English.
AB   Adenosine, released by cells in an injurious or hypoxic environment,
     possesses potent anti-inflammatory effects by inhibiting the production of
     proinflammatory cytokines and superoxide anions (O2-).  We hypothesized
     that adenosine compounds also induced heterologous desensitization of
```

chemokine receptors, which played a critical role in leukocyte trafficking. Our studies using **adenosine receptor** subtype-specific agonists revealed that pretreatment with adenosine compounds suppressed RANTES-induced chemotaxis and Ca2+ flux through activation of A2a **adenosine receptor**. Adenosine compounds also desensitized IL-8- and MCP-1-induced chemotaxis, but not that induced by fMLP. Activation of protein kinase A (PKA), a component of the signaling pathway induced by the A2a receptor, was sufficient to desensitize RANTES-induced chemotaxis. Inhibition of PKA reversed the desensitization effects of adenosine compounds, suggesting that PKA was necessary for A2a receptor-mediated heterologous desensitization. In a mouse model, prior activation of A2a receptors blocked RANTES-induced recruitment of leukocytes in an air pouch. Moreover, the A2a receptor-induced cross-desensitization also reduced the susceptibility of monocytes to infection by an R5 strain of **HIV**-1. Our results suggest that activation of A2a **adenosine receptors** suppresses chemokine receptor function, and such receptor cross-talk was based on the simple mechanism of PKA-mediated heterologous desensitization, thus contributing to the antiinflammatory activity of adenosine.

L33 ANSWER 2 OF 5 MEDLINE on STN

2006013188. PubMed ID: 16371225. Purine P1 receptor-dependent immunostimulatory effects of antiviral acyclic analogues of adenine and 2,6-diaminopurine. Kmonickova Eva; Potmesil Petr; Holy Antonin; Zidek Zdenek. (Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague.. kmonickova@biomed.cas.cz) . European journal of pharmacology, (2006 Jan 13) Vol. 530, No. 1-2, pp. 179-87. Electronic Publication: 2005-12-20. Journal code: 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB Acyclic nucleoside phosphonates are widely recognised antivirals. The oral prodrugs of prototype compounds, e.g., 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA; adefovir), and 9-(R)-[2-(phosphonomethoxy)propyl]adenine [(R)-PMPA; tenofovir] were approved by FDA for treatment of hepatitis B (Hepsera), and acquired immunodeficiency syndrome (AIDS) (Viread), respectively. A number of acyclic nucleoside phosphonates possess immunostimulatory activity. The present experiments demonstrate that activation of cytokine and chemokine secretion is mediated by **adenosine receptors**. Included in the study were 9-(R)-[2-(phosphonomethoxy)propyl]adenine [tenofovir], N(6)-cyclopentyl-(R)-9-[2-(phosphonomethoxy)propyl]-2,6-diaminopurine, N(6)-cyclopropyl-(R)-9-[2-(phosphonomethoxy)propyl]-2,6-diaminopurine, and N(6)-isobutyl-9-[2-(phosphonomethoxy)ethyl]-2,6-diaminopurine. All of them activate secretion of tumor necrosis factor-alpha (TNF-alpha), interleukin-10 (IL-10), "regulated on activation of normal T cell expressed and secreted" (RANTES/CCL5), and macrophage inflammatory protein-1alpha (MIP-1alpha/CCL3) in murine macrophages. With exception of MIP-1alpha, the effects were inhibited by antagonists of adenosine A(1), A(2B), and A(3) receptors (not by adenosine A(2A) receptor antagonist). The adenosine A(1) receptor antagonist inhibited TNF-alpha, IL-10, and RANTES, adenosine A(2B) receptor antagonist inhibited TNF-alpha and RANTES, and adenosine A(3) receptor antagonist inhibited IL-10 and RANTES. The suppression is due to decreased transcription of cytokine mRNA. It may be suggested that acyclic nucleoside phosphonates are nonspecific ligands for purine P(1) receptors.

L33 ANSWER 3 OF 5 MEDLINE on STN

2004606421. PubMed ID: 15579287. Acquired neuronal channelopathies in **HIV**-associated dementia. Gelman Benjamin B; Soukup Vicki M; Schuenke Kimberly W; Keherly Michael J; Holzer Charles 3rd; Richey Frances J; Lahart Christopher J. (Texas NeuroAIDS Research Center Department of Pathology, Rt 0785, University of Texas Medical Branch, Galveston, TX 77555-0785, USA.. bgelman@utmb.edu) . Journal of neuroimmunology, (2004 Dec) Vol. 157, No. 1-2, pp. 111-9. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB A gene expression profile of the human brain cortex was performed in people with **HIV**-1-associated dementia (HAD) using Affymetrix HG-U133 chips. Messenger RNA transcripts in middle frontal gyrus from subjects with HAD or milder neurocognitive dysfunction were compared to **HIV**-negative people. The analysis focused on ionic conductance carriers that control membrane excitation. Overexpressed ionic channel genes in brain cortex of subjects with dementia included (1) a calcium-driven K+ channel that prolongs afterhyperpolarization (AHP) current, (2) a leak type of K+ channel that prolongs the AHP, (3) an **adenosine receptor** that modulates cationic current via G proteins, (4) a G protein-coupled serotonin receptor that modulates cyclic AMP-linked current transduction,

(5) a G protein-coupled dopamine receptor, (6) a GABA receptor subunit that conducts chloride current. Underexpressed current generators in the demented subjects included (1) two voltage-gated K+ channels that influence refractory periods and the onset of AHP, (2) a Na+ channel subunit that modifies current inactivation and the onset of the AHP, (3) a neuronal type of voltage-sensitive Ca+ channel that controls postsynaptic membrane excitability, (4) a metabotropic glutamate receptor that regulates cationic gating via G protein coupling, (5) A specific Galpha protein that transduces metabotropic cationic current, (6) an NMDA receptor subunit, (7) a glycine receptor subunit that modulates chloride current. These gene expression shifts probably occurred in neurons because they were not present in gyral white matter. Acquired neuronal channelopathies were not associated with a generalized shift of neuronal or glial cell markers, which suggest that they were not an artifact produced by neurodegeneration and/or glial cell proliferation. Channelopathies were not correlated with a generalized increase of inflammatory cell transcripts and were present in demented people without, and with **HIV** encephalitis (HIVE). We surveyed experimentally induced perturbations of these channels to determine the implications for brain function. Eleven experimental channelopathies produced decreased neuronal firing frequencies and pacemaker rates in model neurons; seven channelopathies increase neuronal firing rates experimentally. The implied disruption of neuronal excitability is consistent with some features of HAD, including its potential reversibility after **HIV**-1 replication is suppressed, the abnormal electroencephalographic recordings, the lack of clear-cut correlation with neurodegeneration and the lack of strict correlation with brain inflammation. The channelopathy concept may have wide relevance to the subcortical dementias.

L33 ANSWER 4 OF 5 MEDLINE on STN

2004444573. PubMed ID: 15351206. **Adenosine receptors** control **HIV**-1 Tat-induced inflammatory responses through protein phosphatase. Fotheringham J; Mayne M; Holden C; Nath A; Geiger J D. (Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, MB, Canada.) Virology, (2004 Oct 1) Vol. 327, No. 2, pp. 186-95. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Recently, adenosine has been proposed to be a "metabolic" switch that may sense and direct immune and inflammatory responses. Inflammation and pro-inflammatory cytokine production are important in development of **HIV**-1 associated dementia, a devastating consequence of **HIV**-1 infection of the CNS. The **HIV**-1 protein Tat induces cell death in the CNS and activates local inflammatory responses partially by inducing calcium release from the endoplasmic reticulum. Because activation of **adenosine receptors** decreases production of the pro-inflammatory cytokine TNF-alpha in several experimental paradigms both in vitro and in vivo, we hypothesized that **adenosine receptor** activation would control both increased intracellular calcium and TNF-alpha production induced by Tat. Treatment of primary monocytes with Tat significantly increased the levels of intracellular calcium released from IP3 stores. Activation of **adenosine receptors** with CGS 21680 inhibited Tat-induced increases of intracellular calcium by 90 +/- 8% and was dependent on protein phosphatase activity because okadaic acid blocked the actions of CGS 21680. Tat-induced TNF-alpha production was inhibited 90 +/- 6% by CGS 21680 and concurrent treatment with okadaic acid blocked the inhibitory actions of CGS 21680. Using a model monocytic cell line, CGS 21680 treatment increased cytosolic serine/threonine phosphatase. Together, these data indicate that A2A receptor activation increases protein phosphatase activity, which blocks IP3 receptor-regulated calcium release and reduction of intracellular calcium inhibits TNF-alpha production in monocytes.

L33 ANSWER 5 OF 5 MEDLINE on STN

1999401186. PubMed ID: 10469881. Structure-based drug design: combinatorial chemistry and molecular modeling. Kirkpatrick D L; Watson S; Ulhaq S. (ProlX Pharmaceuticals, Inc., Pittsburgh, PA, USA.. Lynn.Kirkpatrick@uregina.ca) . Combinatorial chemistry & high throughput screening, (1999 Aug) Vol. 2, No. 4, pp. 211-21. Ref: 54. Journal code: 9810948. ISSN: 1386-2073. Pub. country: Netherlands. Language: English.

AB Drug discovery efforts are shifting to include the rapid synthetic procedures of combinatorial chemistry and the elegance of rational library design. The wealth of computational methods which explore both the receptor structure and the ultimate pharmacophore complementarity, provide novel avenues for chemists to discover new lead compounds or design virtual libraries for screening prior to the synthetic stage. This

mini-review provides an overview of a few current methodologies of library generation, highlighting docking procedures which have utility in both the discovery and optimization stages of drug development. Three specific examples of different approaches to the use of docking are provided. These describe the development of inhibitors to the human A3 **adenosine receptor** and **HIV**-1 protease, and the evaluation of the activity of novel inhibitors of the redox regulator protein, human thioredoxin.

```
=> d his

     (FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

     FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
                E WILSON CONSTANCE N/IN
L1               3 S E4

     FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
                E WILSON C N/IN
L2              19 S E3
L3               8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
                E WILSON C N/AU
L4              96 S E3
L5               1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6            2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7            1803 S L6 AND ANTAGONIST?
L8             319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9             140 S L8 AND ANTAGONIST?/CLM
L10             61 S L9 AND AY<2002
L11              4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12             57 S L10 NOT L11
L13              1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14             56 S L10 NOT (L11 OR L13)
L15             10 S L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)
L16              1 F FILE WPIDS

     FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
L17            214 S (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)
L18            123 S L17 AND ANTAGONIST?
L19             62 S L18 AND PY<2002
L20              0 S L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOS
L21              2 S L19 AND (IMMUNOLOG?)
L22              1 S L19 AND (INFECT?)

     FILE 'MEDLINE' ENTERED AT 08:28:06 ON 07 JAN 2007
L23           3096 S (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)
L24           2008 S L23 AND ANTAGONIST?
L25           1592 S L24 AND PY<2002
L26              0 S L25 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L27             17 S L25 AND (ADA OR ADENOSINE DEAMINASE DEFICIENCY)
L28              8 S L25 AND REVIEW?
L29           1655 S (P2X RECEPTOR? OR P2-PURINOCEPTOR?)
L30            892 S L29 AND ANTAGONIST?
L31              0 S L30 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADENOSINE DEA
L32         171687 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L33              5 S L32 AND (ADENOSINE RECEPTOR? OR PURINOCEPTOR?)

=> s l32 and (purine receptor?)
           18181 PURINE
          779544 RECEPTOR?
             134 PURINE RECEPTOR?
                 (PURINE(W)RECEPTOR?)
L34            0 L32 AND (PURINE RECEPTOR?)

=> s (adenosine deaminase deficiency)
          155447 ADENOSINE
           11082 DEAMINASE
          226691 DEFICIENCY
L35           332 (ADENOSINE DEAMINASE DEFICIENCY)
                 (ADENOSINE(W)DEAMINASE(W)DEFICIENCY)
```

```
=> s l35 and antagonist?
        542956 ANTAGONIST?
L36          34 L35 AND ANTAGONIST?

=> s l36 and (A1 receptor? or A1 adenosine receptor?)
         22566 A1
        779544 RECEPTOR?
          2451 A1 RECEPTOR?
                 (A1(W)RECEPTOR?)
         22566 A1
        155447 ADENOSINE
        779544 RECEPTOR?
          1002 A1 ADENOSINE RECEPTOR?
                 (A1(W)ADENOSINE(W)RECEPTOR?)
L37           0 L36 AND (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)

=> d his

     (FILE 'HOME' ENTERED AT 07:55:34 ON 07 JAN 2007)

     FILE 'USPATFULL' ENTERED AT 07:56:05 ON 07 JAN 2007
                 E WILSON CONSTANCE N/IN
L1             3 S E4

     FILE 'WPIDS' ENTERED AT 07:56:50 ON 07 JAN 2007
                 E WILSON C N/IN
L2            19 S E3
L3             8 S L2 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'MEDLINE' ENTERED AT 07:58:40 ON 07 JAN 2007
                 E WILSON C N/AU
L4            96 S E3
L5             1 S L4 AND (ADENOSINE RECEPTOR? OR P2? RECEPTOR? OR P2? PURINOCEP

     FILE 'USPATFULL' ENTERED AT 08:00:06 ON 07 JAN 2007
L6          2132 S (ADENOSINE RECEPTOR? OR P2? PURINOCEPTOR? OR P2X RECEPTOR?)
L7          1803 S L6 AND ANTAGONIST?
L8           319 S L7 AND (ADENOSINE RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM OR P
L9           140 S L8 AND ANTAGONIST?/CLM
L10           61 S L9 AND AY<2002
L11            4 S L10 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L12           57 S L10 NOT L11
L13            1 S L12 AND (ADA/CLM OR ADENOSINE DEAMINASE DEFICIENCY/CLM)
L14           56 S L10 NOT (L11 OR L13)
L15           10 S L9 AND (P2X RECEPTOR?/CLM OR P2? PURINOCEPTOR?/CLM)
L16            1 F FILE WPIDS

     FILE 'WPIDS' ENTERED AT 08:24:00 ON 07 JAN 2007
L17          214 S (A1 ADENOSINE RECEPTOR? OR A1 RECEPTOR?)
L18          123 S L17 AND ANTAGONIST?
L19           62 S L18 AND PY<2002
L20            0 S L19 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADA OR ADENOS
L21            2 S L19 AND (IMMUNOLOG?)
L22            1 S L19 AND (INFECT?)

     FILE 'MEDLINE' ENTERED AT 08:28:06 ON 07 JAN 2007
L23         3096 S (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)
L24         2008 S L23 AND ANTAGONIST?
L25         1592 S L24 AND PY<2002
L26            0 S L25 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L27           17 S L25 AND (ADA OR ADENOSINE DEAMINASE DEFICIENCY)
L28            8 S L25 AND REVIEW?
L29         1655 S (P2X RECEPTOR? OR P2-PURINOCEPTOR?)
L30          892 S L29 AND ANTAGONIST?
L31            0 S L30 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS OR ADENOSINE DEA
L32       171687 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L33            5 S L32 AND (ADENOSINE RECEPTOR? OR PURINOCEPTOR?)
L34            0 S L32 AND (PURINE RECEPTOR?)
L35          332 S (ADENOSINE DEAMINASE DEFICIENCY)
L36           34 S L35 AND ANTAGONIST?
L37            0 S L36 AND (A1 RECEPTOR? OR A1 ADENOSINE RECEPTOR?)

=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
```

STN INTERNATIONAL LOGOFF AT 08:38:29 ON 07 JAN 2007